Health status, psychological distress and inflammation in heart failure

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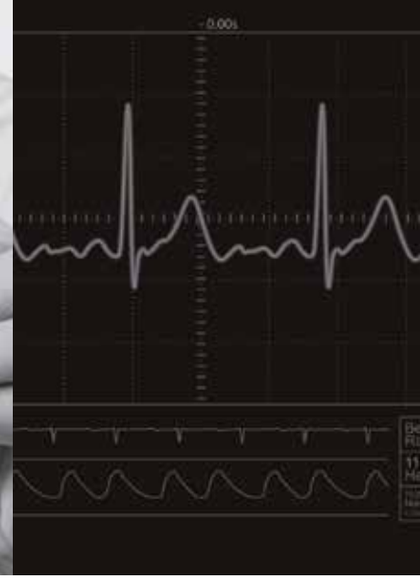






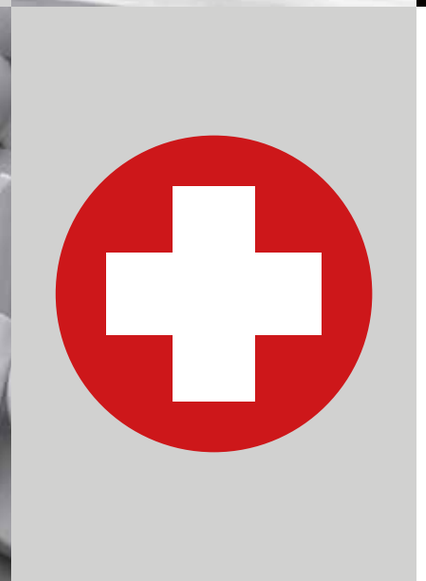

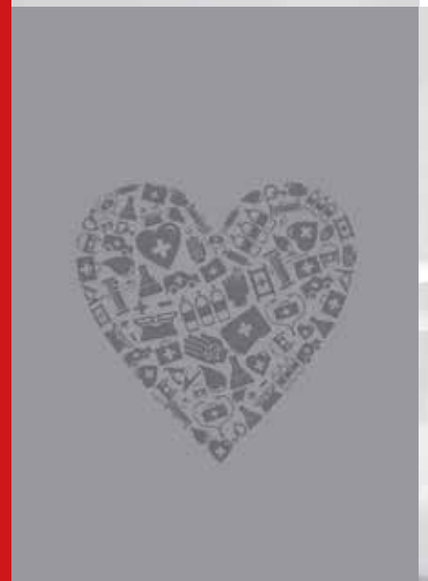

HEALTH STATUS, PSYCHOLOGICAL DISTRESS AND INFLAMMATION IN HEART FAILURE: TOWARDS A PATIENT-CENTERED APPROACH

Corline Brouwers

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Center of Research on Psychology in Somatic diseases

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Health status, Psychological Distress and Inflammation in Heart Failure:

Towards a Patient-Centered Approach

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“We have bigger houses, but smaller families. More conveniences, but less time. We have knowledge, but less judgments; more experts, but more problems; more medicines but less health.” — Dalai Lama XIV




CHAPTER 1

General Introduction

Heart failure: disease and diagnosis

Heart failure is a major public health issue worldwide that is associated with increased disability and mortality.[1] Currently, the prevalence of heart failure in the Western world is estimated at 2-3% and there are over 23 million people suffering from heart failure worldwide.[2-4] The prognosis of heart failure is poor, with only 25-35% of heart failure patients surviving beyond 5 years after diagnosis.[5, 6] Due to the ageing of the population and the improved survival of heart failure patients, the number of heart failure patients is expected to increase even further in the future, placing a high burden on patients and their families as well as on society at large.[7, 8]

Heart failure is a complex clinical syndrome which is characterized by an abnormality of the cardiac structure or function, leading to failure of the heart to deliver oxygen at a rate commensurate with the requirements of the metabolizing tissues.[9] Common causes of heart failure include myocardial infarction, hypertension, valvular heart disease, viral infection, exposure to toxins, chemotherapy and cardiomyopathy. Some cardiomyopathies have genetic underpinnings, such as hypertrophic and non-compaction cardiomyopathy, while most others are acquired. The cardinal manifestations of heart failure differ based on the underlying cause and may include symptoms and signs such as dyspnea, fatigue, elevated jugular venous pressure, pulmonary crackles, and displaced apex beat.[10]

Diagnosing heart failure can be difficult, especially in the early stages. Although symptoms alert patients to seek medical attention, many heart failure symptoms are non-specific and do therefore not help discriminate between heart failure and other conditions.[10] Routine tests for diagnosing suspected heart failure are an echocardiogram, electrocardiogram, chest X-ray and routine laboratory tests. A laboratory test for heart failure which has emerged in the last 10-15 years is the measurement of cardiac hormones, such as natriuretic peptides. Natriuretic peptides are markers of neurohormonal activation which are secreted by cardiomyocytes when the heart is diseased or the load on any chamber is increased. The two most commonly used natriuretic peptides are B-type natriuretic peptide (BNP) and N-terminal pro B-type natriuretic peptide (NT-proBNP).[10-12] Increased BNP levels have been shown to be strong indicators for a poor prognosis, but also to be of value in guiding therapy to treat heart failure.[13]

Heart failure is usually a progressive disease, caused by cardiac remodeling of the wall of the left ventricle. Heart failure can be divided into different stages, with specific treatments being available at each stage to relieve symptoms, prevent hospital admission, and improve survival.[1] Pharmacological therapy, including vasodilators, angiotensin-converting-enzyme inhibitor (ACE)-inhibitors and beta-blockers, are usually the first line of treatment, followed by more rigorous medical interventions such as a percutaneous coronary intervention, coronary artery bypass grafting, implantation of an implantable cardioverter defibrillator with or without cardiac resynchronization therapy (i.e. ICD or CRT-D), a left ventricular assist device (LVAD) or heart transplantation.

ICD/CRT-D

An ICD is a small battery-powered electrical impulse generator that constantly monitors the rate and rhythm of the heart and can deliver therapies by means of anti-tachycardia pacing or a low- or high-voltage electrical shock to abort potentially life-threatening arrhythmias.[14] The ICD is the first choice of treatment for the prevention of sudden cardiac death due to potentially life threatening ventricular arrhythmias, since clinical trials have demonstrated its superiority over anti-arrhythmic therapy.[15-17] ICD therapy can be indicated as primary or secondary prevention. Secondary prevention is indicated in patients who survived an initial sudden cardiac arrest, while primary prevention is indicated in patients who did not experience prior life-threatening arrhythmias but who are considered at high risk. A reduction in mortality of 26% and 28% was found with ICD therapy compared to anti-arrhythmic drugs for primary and secondary prevention, respectively.[15, 17]

Approximately one third of patients with heart failure suffer from a prolonged QRS duration (>120 ms), which leads to a disruption of the normal, coordinated and simultaneous distribution of the electrical signal to the two ventricles. For these patients, cardiac resynchronization therapy (CRT) may be indicated, which helps to restore left ventricular systolic function by correcting the electro-mechanical dyssynchrony, thereby facilitating that blood is pumped throughout the body more efficiently. In addition, CRT has been shown to improve exercise capacity and to reduce rehospitalization and mortality.[16, 18,19] A CRT device can be combined with an ICD, also called a CRT-D, combining the separate functions of both devices **(Figure 1).** [20]

Figure 1: CRT-D[21]

Left ventricular assist device (LVAD)

Driven by the significant shortage of donor hearts and a simultaneous increase in the incidence of heart failure, LVADs are becoming an indispensible tool for patients with advanced heart failure whose medical treatment options have been exhausted.[22] LVADs are mechanical circulatory implantable devices that are used to partially or completely replace the function of a failing heart by maintaining blood circulation and vital organ perfusion.[23] Some LVADs are intended for short term use, typically for patients recovering from a heart attack or heart surgery, while others are intended for long-term use (months to years and in some cases for life) for patients suffering from advanced heart failure. Long-term use of LVADs is either as a bridge to transplantation (BTT) in transplant candidates who show considerable clinical deterioration and are unable to wait any longer for heart transplantation, or as an alternative for heart transplantation (DT).[24] In the Netherlands the use of LVAD therapy as BTT is expanding, however the use as DT is currently only allowed on a small scale with stringent criteria.

The first generation of LVADs are pulsatile pumps that mimic the natural pulsing action of the heart. These devices demonstrated to be superior with respect to survival compared to optimal medical treatment, with a reduction of 48% in mortality.[25] However, due to their large volume and design a large dissection was required for implantation, with the result being that the device could not be implanted in patients with a small body size (Body Surface Area $<1.5m^2$).

In the last decade, several new devices have become available offering a greater durability and longevity. These devices are continuous flow pumps that can be subdivided into either centrifugal or axial flow pumps **(Figure 2)**.[26] To date, more than 6000 patients are implanted with a continuous flow pump. Among the continuous flow pumps, actuarial survival is 80% at 1 year and 70% at 2 years.[27]

Figure 2: Centrifugal LVAD pump (HeartWare®)[22] and axial LVAD pump (HeartMate II®)[28]

The impact of heart failure on health status and psychological distress

Heart failure can have a tremendous impact on patients' lives due to restrictions in functional capacity and a negative effect on social relationships, financial status and psychological well-being.[29, 30] As a result, many heart failure patients report impaired health status.[31,32] Health status is a multidimensional concept which assesses the patient's perception of how a disease or treatment affects his/her symptoms and functioning.[33]

Furthermore, patients with heart failure are disproportionately afflicted with psychological distress and psychiatric disorders, such as depression, anxiety and post-traumatic stress.[34] Depression is a mood disorder that interferes with a person's ability to perform his or her day-to-day functioning, while anxiety is a negative affective state resulting from an individual's perception of threat that is characterized by a perceived inability to predict, control, or gain the preferred results in given situations.[34] The prevalence of depression and anxiety in heart failure patients ranges from 15-40%.[35]

Heart failure and its treatment options (i.e., CRT-D and LVAD) may also qualify as traumatic due to their potential life-threatening nature that may be associated with intense

fear, persistence of painful intrusive memories, avoidance behavior and hyperarrousal, which is also known as post-traumatic stress disorder.[36] In heart failure populations, 10-17% of patients suffer from post-traumatic stress.[37]

Symptoms of depression, anxiety and post-traumatic stress can be disabling, and are associated with increased risk for declines in physical health, mortality, higher medication costs, non-compliance with treatment, hospital readmissions and lack of adoption of secondary prevention behaviors, such as smoking cessation, physical activity, and cardiac rehabilitation.[38]

Due to their potential impact on heart failure outcomes, health status and psychological distress are receiving increased recognition and are more often included as patient-reported outcomes in large clinical trials in addition to the clinical cardiovascular endpoints.[39] Furthermore, there is a growing belief that patient-reported outcomes are as valid as the clinician's perspective due to the acknowledgement that an illness and its treatment affect all domains of a patient's life and not merely physical health.[40] Information on patient-reported outcomes cannot be extracted from patients' medical records or a proxy, emphasizing the importance of assessing PROs in their own right using self-report questionnaires. The questionnaires used for measuring patient-reported outcomes are either disease-specific or generic, thereby making it possible to compare outcomes with other heart failure patients, other disease groups, or healthy individuals, depending on the type of measure chosen.[41] By measuring patient-reported outcomes in a structural manner, they may provide important additional information to health care providers and serve as targets for intervention in individual patients, with the potential to improve patient-centered care.[39, 42]

The association between psychological distress and clinical outcomes of heart failure

It is not well understood how psychological distress is linked to adverse clinical outcomes in patients with heart failure. Although some advocate that negative emotions may be a risk factor for heart failure, others suggest that heart failure may elicit psychological distress or that an interactional effect exists whereby negative emotions and heart failure affect one another in deleterious ways.[34] Several mechanisms have been proposed that may explain the link between psychological distress and adverse clinical outcomes in heart failure patients. These can be divided into two categories, namely *behavioral* and *physiological*

mechanisms. Behavioral mechanisms include unhealthy lifestyle habits (e.g. smoking and not engaging in exercise) and poor medication adherence.[43-45] Furthermore, impaired cognitive focus, reduced energy, and motivation associated with psychological distress might affect patients' willingness and ability to follow through with treatment advice and to attend scheduled hospital appointments.[46] Pathophysiological mechanisms constitute changes in cardiac rhythm, abnormal cardiac autonomic tone,[47] increased platelet aggregation,[48] comorbidities and alterations in the hypothalamus-pituitary-adrenal (HPA) axis. In addition, inflammation is an acknowledged physiological mechanism through which distress may affect heart failure progression.[49]

Inflammation

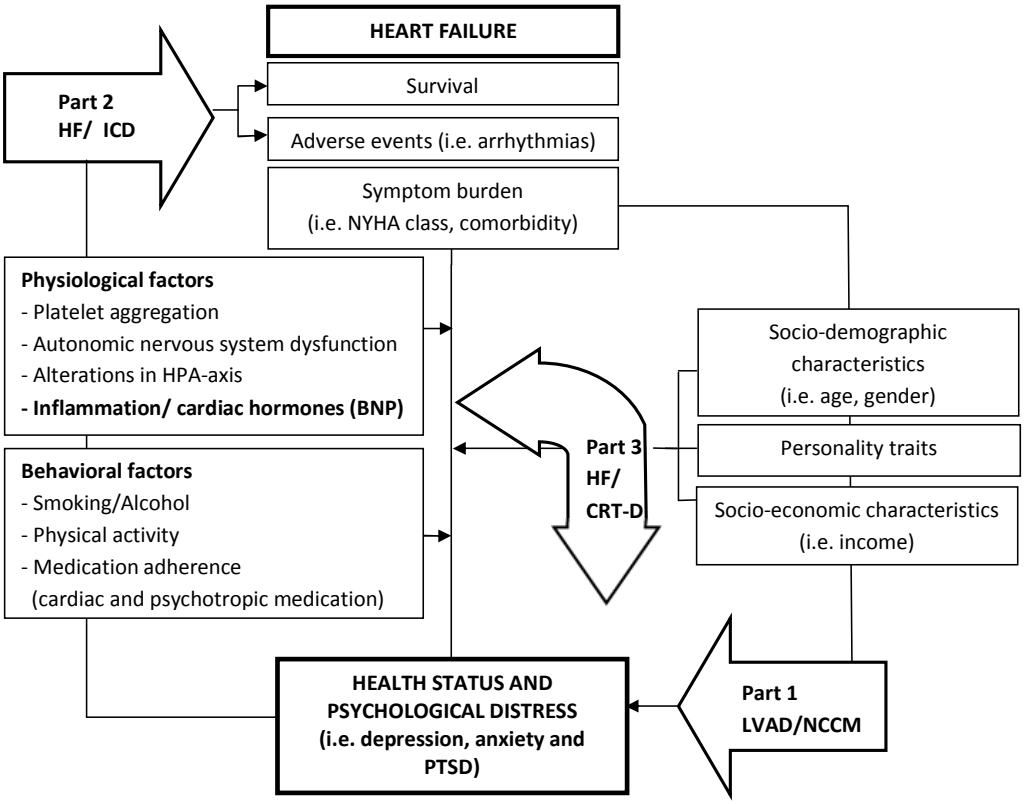
Inflammation is part of the biological response of vascular tissues to harmful stimuli such as pathogens but also to distress and chronic illness.[49] Important regulators of inflammation are called cytokines, which are soluble peptides that can mediate cell-to-cell interactions via specific cell surface receptors and regulate the activation, differentiation, death or acquisition of effector functions of the immune system. In addition, they mediate effects of the cells of the immune system on other cells and tissues.[50] Through complex physiological pathways depression can stimulate pro-inflammatory cytokine release which exerts a deleterious effect on the heart by suppressing cardiac contractility, increasing the degree of atherosclerosis (plaque in artery walls) and by impeding cardiac remodeling.[49, 51-53] The most common cytokines which are used as indicators of inflammation are tumor necrosis factor (TNF)-α, soluble TNF receptors 1 and 2 (sTNFr1 and sTNFr2), interleukin (IL)-6 and high sensitive C-reactive protein (hsCRP). Evidence has also been found for a reversed association in which inflammation is induced by heart failure, which can - when being exacerbated in duration and intensity - lead to a state of depression.[54,55] This form of depression is characterized by somatic depressive symptoms[56] and often referred to as sickness behavior.[57]

Aims and outline of this dissertation

The current dissertation focuses on health status and psychological distress, and their association with cardiovascular outcomes and inflammation, in different samples of heart failure patients. **Figure 3** provides an overview of the dissertation and a conceptual model of

how psychological distress and health status are linked to prognosis via physiological and behavioral pathways that may be influenced by patient-related factors such as personality, socio-demographic and socio-economic characteristics and disease severity.

Figure 3: Schematic outline of the association between patient well-being and heart failure



Part one: Health status and psychological distress in patients with heart failure

The first part of this dissertation addresses the health status and psychological distress of patients after implantation with an LVAD or in patients who are genetically predisposed for heart failure. **Chapter 2** provides an overview of the knowledge on health status and psychological distress in patients implanted with a LVAD, thereby making a distinction between the first and second generation of devices. **Chapters 3 and 4** elaborate on this topic and report on the results of a prospective multicenter study on health status and psychological distress, and their predictors, in LVAD patients and partners over time.

Chapter 5 examines the differential impact of genetic vulnerability versus disease severity in patients diagnosed with non-compaction cardiomyopathy, using a cross-sectional case-control design.

Part two: Psychological distress and clinical outcomes in heart failure

Psychological distress is associated with increased risk for morbidity and mortality in patients with heart failure, but little is known about the mechanisms that may explain this link. It is also not clear whether treating psychological distress in heart failure patients, by means of psychological interventions, psychotropic medication or a combination thereof, will enhance survival. **Chapter 6** examines the prevalence of anti-depressant use 5-years post heart failure diagnosis in a large sample of patients from the Danish heart failure registries. Furthermore, this chapter reports on the predictors of anti-depressant use and the relation between anti-depressant use and all-cause mortality. **Chapter 7** is a systematic review that evaluates the evidence for a link between psychological vulnerability, ventricular tachyarrhythmias, and mortality in patients with an ICD, and the physiological and behavioral pathways that may explain this link.

Part three: Health status and psychological distress - the link with inflammation and cardiac hormones

Cardiac hormones, such as brain natriuretic peptides, are markers of disease severity and valuable prognostic indicators in heart failure. Knowledge of the extent to which psychological distress in heart failure patients is associated with indicators of disease severity is important, as an association between both may indicate that psychological distress is confounded by disease severity and would then be a risk marker for prognosis rather than a risk factor. **Chapter 8** examines the link between brain natriuretic peptide and the continuous and dichotomized scores of a broad range of psychological risk markers in a Danish cohort of heart failure patients.

Evidence suggests that inflammation is one of the mechanisms through which psychological distress may adversely affect clinical outcomes in heart failure patients, or vice versa. To examine the directionality of this association, **Chapter 9** explores inflammation as one of the potential explanatory models for depression in heart failure, together with markers of disease severity and psychological vulnerability. **Chapters 10 and 11** show that

inflammation is not only linked to psychological distress, but also to positive measures of psychological and physical well-being in heart failure patients. **Chapter 10** is based on the assumption that positive affect can act as a potential protective factor in the progression of chronic disease through a positive effect on inflammation. As there is an ongoing debate on the core characteristics of positive affect and how it should be measured, this chapter compares three different measures for positive affect and their association with inflammation in a sample of patients with chronic heart failure. **Chapter 11** examines whether a significant clinical improvement after CRT-D implantation, based on an absolute increase in health status and decrease in echo parameters, is associated with a decrease in inflammation.

In **Chapter 12** the main findings of this dissertation will be discussed and implications for future research and clinical practice will be outlined.

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PART ONE

Health status and psychological distress in patients with heart failure

CHAPTER 2

Patient reported outcomes in left ventricular assist device therapy: A systematic review and recommendations for clinical research and practice

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ABSTRACT

Background: Technological advancements of left ventricular assist devices (LVAD) have created today's potential for extending the lives of patients with end stage heart failure. Few studies have examined the effect of LVAD therapy on patient-reported outcomes (PROs) such as health status, quality of life and anxiety/depression, despite poor PROs predicting mortality and rehospitalization in heart failure patients. In this systematic review we provide an overview of available evidence on the impact of LVAD therapy on PROs, and discuss recommendations for clinical research and practice.

Methods and Results: A systematic literature search identified 16 quantitative studies with a sample size n≥10 (mean±SD age=50.1±12.6 years) that examined the impact of LVAD therapy on PROs using a quantitative approach. Initial evidence suggests an improvement in health status, anxiety and depression in the first few months following LVAD implantation. However, PRO scores of LVAD patients are still lower with respect to physical, social, and emotional functioning as compared to transplant recipients. These studies had several methodological shortcomings, including the use of relatively small sample sizes, and only a paucity of studies focused on anxiety and depression.

Conclusions: There is a paucity of studies on the patient perspective of LVAD therapy. To advance the field of LVAD research and to optimize the care of an increasingly growing population of patients receiving LVAD therapy, more well-designed large-scale studies are needed to further elucidate the impact of LVAD therapy on PROs.

INTRODUCTION

Worldwide heart transplantation offers hope to approximately 3,500 advanced heart failure patients each year, but there are still over 15,000 patients on transplant waiting lists in urgent need of a donor heart.[1] Driven by this significant shortage of donor hearts and a simultaneous increase in the incidence of heart failure, the first concepts of mechanical circulatory support from the early 1970s have been transformed into highly advanced devices capable of long-term support for patients with end stage heart failure. The most commonly used long-term devices are left ventricular assist devices (LVADs).[2, 3] LVADs can be divided into 2 main types – (i) the pulsatile pumps that mimic the natural pulsing action of the heart and (ii) the continuous flow pumps which can be subdivided into either centrifugal pumps or axial flow pumps.[4]

The primary focus of the majority of LVAD studies has been on the clinical aspects of this therapy, including the efficacy of different device types, device settings, and alternative therapies (e.g., optimal medical treatment and heart transplantation) in enhancing survival and reducing complications. Only a subset of LVAD studies have examined the impact of LVAD therapy on patient reported outcomes (PROs), such as health status.[5] This is unfortunate, because PROs can be used to assess the effectiveness of treatment, to enhance the quality of care and management of patients, and to help allocate resources to patients who need it the most.[6,7] In addition, poor health status has predicted mortality and rehospitalization in patients with coronary artery disease and heart failure independent of traditional biomedical risk factors.[8] This information cannot be extrapolated from information standardly available in patients' medical records nor from a proxy.[7, 9] In addition to health status, LVADs may also have an effect on psychological morbidity and feelings of worry and stress.[10-14] Device type and settings might influence the level of psychological morbidity because patients receiving pulsatile LVAD therapy have a higher rate of complications, and are bothered by the clicking noise of the device.[15] In other heart failure populations, psychological morbidity has been associated with poor treatment adherence, poor self-efficacy, and an unhealthy lifestyle.[15,16] Yet, it is not known whether LVAD patients with psychological problems are identified and, hence, treated.

In the future, LVAD therapy is likely to be indicated as bridge to transplant and as destination therapy worldwide, thereby providing much optimism for the treatment of more heart failure patients in the future.[17] To optimize the management of this growing group of

patients, we need to know the impact of LVAD therapy on patients from a patient perspective.[12] Only with such knowledge are we able to improve the care after LVAD implantation and provide patients and families with all the necessary information that they need for effective decision-making regarding whether LVAD implantation is aligned with their own preferences and goals.

Hence, the objectives of this systematic review are to provide a detailed overview of available evidence on the impact of LVAD therapy on PROs, and suggest recommendations for clinical research and practice.

METHODS

Literature search

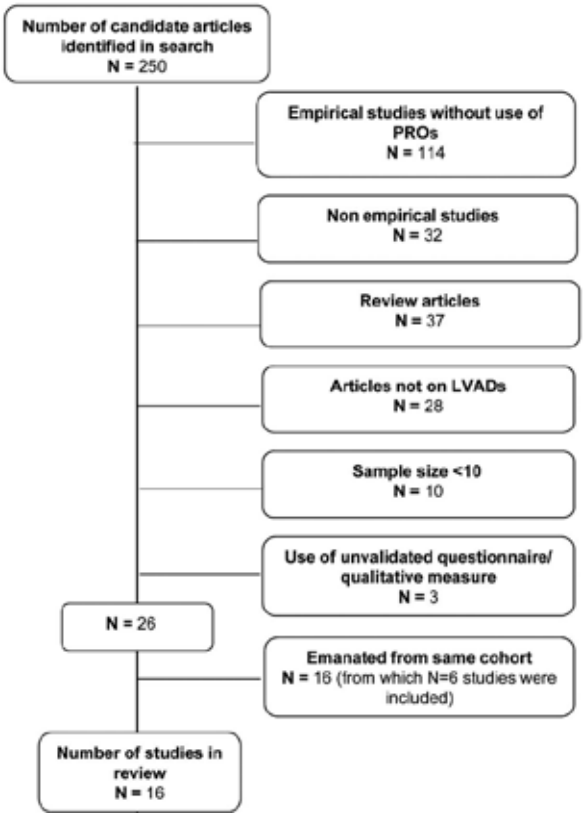
The first author (CB) performed a literature search on Pubmed in the period from January 1980 to May 2011 using a combination of the following search terms: *LVAD, left ventricular assist device, anxiety, depression, health status, quality of life, emotional distress, psychological distress, psychological morbidity* and *psychosocial.* Only full-text, empirical studies with a sample size of n>10, examining the impact of LVAD therapy on PROs assessed by means of standardized clinical interviews or standardized and validated questionnaires were eligible for inclusion. Articles found by reference searching and articles for which inclusion was questionable were checked by the last author (S.S.P.), after which a consensus was reached between both authors (C.B. and S.S.P.). Of the 250 candidate articles, 26 articles were identified which matched the inclusion criteria. Sixteen studies emanated largely from the same 4 cohorts, as reported on in 1 of the other articles.[10-14, 18-28] From each cohort, only the most recent paper was included (i.e., papers with the most optimal study design and largest sample size), except for 2 extra papers that compared 2 groups of LVAD patients on 2 different devices.[12, 18, 19, 25-27] Hence, the current review is based on 16 studies **(Figure 1).**

Literature overview

Detailed information on the 16 studies included in this review are presented in **Table 1** and **Table 2.** The descriptives data are stratified by studies on pulsatile **(Table 1)** vs. continuous-flow **(Table 2)** devices. Studies in which patients received therapy via both pulsatile and continuous-flow devices were included and were placed in the continuous-flow device table.

For the pulsatile devices, the median number of patients included in the 7 studies was 30 (mean±SD, 36.0±27.2) with the number of patients receiving therapy via LVADs ranging from 10 to 78. The proportion of men ranged from 60% to 99%, and the mean age of study participants was 47.0±13.5 (range, 29-67) years. Three studies (42.9%) used a cross-sectional study design,[29-31] 4 studies (57.1%) a prospective (comparative) study design,[12, 26, 32, 33] of which 2 studies (28.6%) were a randomized controlled trial.[33, 34] In most studies, the baseline assessment was conducted before hospital discharge, which varied between 1 and 2 weeks[12] to approximately 1 month post LVAD implantation.[32] The 3 cross-sectional studies used a variety of assessment times ranging from <6 weeks after implantation[29, 30] to up to 2 months post LVAD implantation.[31] Two studies[26, 32] compared the PROs of LVAD patients with transplant recipients or patients receiving optimal medical treatment. Of all studies, 4 studies (57.1%) focused on health status,[12, 26, 32, 33] 2 (28.6%) on anxiety,[30, 32] and 5 (71.4%) on depression,[26, 29-32] ; 2 (28.6%) studies focused on both anxiety and depression.[30, 32]

Figure 1: Flow chart of article selection



For the continuous-flow devices, the median number of patients included in the 9 studies was 41 (mean±SD, 201±229.5) with the number of LVADs patients ranging from 17 to 655. The proportion of men ranged from 76% to 100% across studies, and the mean±SD age of study participants was 51.5±15.7 (range, 46-62.5) years. Two studies (22%) used a cross-sectional study design,[19, 35] 1 study used a retrospective design (11%),[36] and 6 studies (66.7%) a prospective (comparative) study design.[18, 25, 27, 37-39] The prospective studies performed the baseline assessment within 1 month after LVAD implantation. The retrospective study assessed PROs at 12 months after LVAD implantation,[36] and the cross-sectional studies included patients ranging from 2 to 135 months after LVAD implantation.[19, 36] Two studies compared the PROs of LVAD patients with their partners or with transplant recipients.[19, 37] Of all studies, 8 studies (88.8%) focused on health status,[18, 25, 27, 35-39] while one study (11%) focused on depression.[19]

RESULTS

PROs in studies on pulsatile devices

The studies on the first generation of pulsatile LVADs (Thoratec TCI, Heartmate VE/IP [Thoratec Inc, Pleasanton, California, USA], Novacor LVAS [WorldHeart Inc., Oakland, California, USA], EXCOR [Berlin Heart AG, Berlin, Germany] or Toyobo LVAD [Toyobo Ventricular Assist Systems, Toyobo, Osaka Japan] assessed health status using a prospective design with a variety of instruments **(Table 1)**. All studies found a significant improvement in the mean health status score (i.e. the Minnesota Living with Heart Failure Questionnaire [MLHFQ]) or in at least 2 subdomain scores (i.e., the Short Form Health Survey 36 [F-36], the Sickness Impact Profile, the LVAD stressor scale, and the Quality of Life Index [QoL Index]) at follow-up compared to baseline. The improvement in health status did seem to reach a plateau at ≈3 months after LVAD implantation. The results showed that, during this period, physical disability becomes less prominent and patients feel less fatigued and sleep better, thereby increasing the ability of self-care and ambulation.[12] The impact of the degree of physical disability on health status was also indicated in a recent trial that randomized LVAD patients to an exercise-training programme versus usual care. The outcomes demonstrated that improvement in physical exercise capacity in patients in the treatment arm led to a better health status compared to that of the patients in the control arm.[33]

Despite improvements in physical functioning, many patients may experience psychosocial problems and impaired psychological well-being, especially at around month after implantation.[12, 21] The psychological symptoms seem to originate from feelings of sadness, helplessness, irritability, feeling useless to others and having a sense of loss of control over one's life;[12, 21] and seem to be associated with worrying about LVAD malfunction, complications, waiting for a donor heart and being away from family.[12] Depression and anxiety are correlated with LVAD noise, driveline problems, and infection ($P<0.05$ for all).[30] The prevalence rates of anxiety and depression varied widely across the 6 studies that included a semi-structured diagnostic interview using the Diagnostic and Statistical Manual of Mental Disorders (4th Edition), the Symptom Checklist-90, the Beck Depression Inventory, or the Mini Mental State Examination. Some studies found that only 2% of LVAD patients experienced depression and only 4% experienced anxiety,[20] whereas others found a considerable group of LVAD patients experiencing a depressive or adjustment disorder (21% and 37-50%, respectively).[29, 31]

In trials (i.e. the Randomized Evaluation of Mechanical Assistance in the Treatment of Congestive Heart Failure) comparing LVAD patients on pulsatile devices with patients using optimal medical treatment and transplant recipients, LVAD support was associated with a significant improvement in health status and depressive symptoms in contrast to medication alone ($P<0.05$ for both).[26, 30, 32] However, LVAD patients do not seem to attain the same level of health status compared with transplant recipients, with transplant recipients experiencing more improvements in mobility, self-care ability, physical ability and social functioning than LVAD patients.[13, 32]

Patient reported outcomes in studies on continuous-flow devices

The most intensively studied continuous-flow device used in the studies included for the review was the HeartMate II (Thoratec Inc). Other devices included the Micromed DeBakey (Micromed Cardiovascular Inc., Houston, TX), INCORE (Berlin Heart AG), Jarvik 2000 (Jarvik Heart, Inc., New York, NY), or HVAD device (HeartWare Inc., Framingham, MA) **(Table 2)**. Almost all studies on patients with a continuous-flow LVAD show significant improvements in mean health status scores, using the MLHFQ, Kansas City Cardiomyopathy Questionnaire (KCCQ), SF-36, and EuroQol EQ-5D (EQ-5D), from baseline up to 3-, 6- and 12-month follow-up ($P<0.05$ for all).[18, 25, 27, 35, 36, 38, 39] Only the study by Kugler et al.[37] found no significant

improvement in health status using the SF-36 at the 6 month follow-up. Whether this was due to psychosocial problems or a lower physical exercise tolerance is not clear, because both may ultimately restrict patients' opportunities to re-engage in professional and recreational activities, which are known predictors for long-term health status.[37]

In recent years, several papers have been published on comparative studies between LVAD patients with different devices and in different clinical settings[25, 27, 35, 39] or between LVAD patients and transplant recipients and healthy controls.[37] The HeartMate II trial had 2 arms that enabled the investigators to analyse the health status within and between patients groups supported by the HeartMate XVE or the HeartMate II. At 12-months follow-up the health status of patients receiving therapy via continuous-flow LVADs was better compared with those receiving therapy via pulsatile devices (MLHFQ: P=0.03, KCCC-OSS [Overall Summery Score]: P=0.06, KCCQ-CSS [Clinical Summery Score]: P=0.12)), likely caused by the improved durability, decrease in complications, smaller size and silent operation of the continuous-flow device.[27] Recently, the HeartMate II was also compared with the HeartMate XVE and Thoratec pVAD in a commercial setting to investigate the relative efficacy and risk profile, in patients enrolled in the Interagency Registry for Mechanically Assisted Circulatory Support. Health status appeared to improve equally for the 2 groups of devices (P<0.001) after 3 months to 1 year.[39] Patients receiving therapy via pulsatile and continuous-flow devices were not significantly different on symptoms of anxiety, depression and post-traumatic stress disorder.[19] The cross-sectional study of Meyer et al.[35] found no significant differences in domain scores between 2 continuous-flow systems: the centrifugal-flow pump Heartmate II and axial-flow pump HVAD.

From both arms of the HeartMate II trial, patients were also selected based on their device indication (i.e. bridge-to-transplant or destination therapy) and compared on paired health status scores. The group of LVAD patients indicated for destination therapy had a higher improvement in median health status scores between baseline and 6 months than the group of LVAD patients indicated for bridge-to-transplant therapy (MLHFQ, -40 vs. -29 points; KCCQ-OSS, 39 vs. 28 points; KCCQ-CSS, 36 vs. 24 points, respectively).[32] In this study, 79% of the bridge-to-transplant patients and 92% of the destination therapy patients with paired data had achieved a clinically meaningful improvement of >5 points in their KCCQ-OSS and KCCQ-CSS scores compared with baseline.[32]

Compared to transplant recipients and healthy controls, LVAD patients reported considerably poorer health status at baseline (P=0.0032) and at 6 months follow-up (P=0.016), especially with respect to mental health and physical functioning,[35, 37] and with respect to the social functioning, role physical functioning, and role emotional functioning domains of the SF-36.[35]

Overall, evidence on the impact of the duration of living with an LVAD, the initial diagnosis, and sex and age disparities in health status is scarce among LVAD patients. Women tend to have been underrepresented in LVAD studies to this date, with one study finding no significant gender differences among LVAD patients (MLHFQ, P=0.661; KCCQ-OSS, P=0.706; KCCQ-CSS, P=0.371).[18]

DISCUSSION

Summarizing the findings

This review indicates that LVAD patients experience an improvement in health status, particularly in the first 3 months after LVAD implantation and discharge. This trend was visible irrespective of the type of device (pulsatile vs. continuous-flow devices) and clinical setting (destination therapy and bridge-to-transplant therapy). Results also indicated that LVAD patients supported by continuous-flow devices and destination therapy show the greatest improvements in health status after implantation.

Few studies have examined the prevalence of anxiety and depression in LVAD patients, in particular in patients receiving therapy via continuous-flow LVADs. Patients supported by pulsatile devices showed relatively high mean depression scores just after LVAD implantation.[26, 29, 31] The retrospective study of Bunzel et al.[19, 20] found no significant difference in depression scores between patients receiving therapy via pulsatile vs. continuous-flow devices while patients supported by pulsatile devices were expected to be more vulnerable to psychological distress, based on the higher rate of complications and the characteristics of the device (e.g. short durability, large size, noise, and large batteries). Hence, these differences in findings could well be explained by sample size limitations in subtype of devices, and the time of collecting data.

The LVAD patients report better health status and fewer symptoms of anxiety and depression when compared to their partners and to patients receiving optimal medical treatment, but not when compared to transplant recipients. In contrast to transplant

recipients, LVAD patients are recurrently reminded of their device due to the need to clean the driveline insertion site and change batteries frequently.[15] Furthermore, organ recipients appear to redefine "normal" life and what it entails after transplantation.[32]

Overall, there was a substantial difference between the studies in the handling and reporting of PROs, depending on whether PROs were assessed as primary or secondary outcomes. In **Table 3**, the details on the number of patients alive from baseline to end of follow-up, the estimated percentage of those patients having PRO data, and the cause of missing data were outlined for all prospective studies assessing health status in LVAD patients. Except for the Randomized Evaluation of Mechanical Assistance in the Treatment of Congestive Heart Failure trial,[26] all studies on pulsatile devices assessed health status as a primary outcome, whereas this only holds true for 1 continuous-flow study.[37] The percentage of PRO data obtained from the patients alive over time was 92% - 100% in the pulsatile device studies and 46%-91% in the continuous-flow device studies. At the end of the full study, this percentage was unchanged for the pulsatile device studies, and 49% - 89% for the continuous-flow device studies. In 2 continuous-flow device studies the follow-up period for the PROs was shorter than the follow-up period for the full study, causing an absence of PRO data at the final time points.[18, 25] For those studies, the percentage of PRO data obtained was calculated based on the patients alive at the end of the PRO follow-up period rather than at the end of the full study. Most studies indicated similar reasons for the missing data (e.g. patient exclusion, deceased, too ill, HTx, dropout). None of the studies reported cognitive limitations or psychological distress as a reason for missing data.

Limitations of the review

Because of the different time era of the studies included in this review and the heterogeneity of the studies (differences in follow-up assessments, sample sizes and PRO assessment), it was not possible to perform a formal meta-analysis. Although increasing the statistical power by excluding studies with a small sample size (n<10), this resulted in fewer articles eligible for inclusion. In turn, this could have potentially created a bias towards results found in larger studies. The proportion of female patients across studies was relatively low; hence, it is not feasible to generalize the findings to women with an LVAD.

There was a considerable difference in the percentage of missing PRO data between the pulsatile and continuous-flow device studies. This is most probably caused by the fact

that most of the pulsatile device studies assessed PROs as primary outcomes but also because of shorter follow-up times, thereby decreasing the chance of death, HTx and drop-out. Only three studies[18, 37, 38] reported how they dealt with the loss of data, which included comparing the baseline characteristics of patients for whom data were and were not available or by substituting the missing scores by the maximum negative score of the used instrument. Correcting for missing data did not affect the outcomes in these studies. Other studies calculated the percentage and significance of improvement by simply comparing the group total scores of patients with paired data between baseline and follow-up. However, the number of patients with paired data decreases significantly over time, which may increase the probability of finding a significant improvement since the sicker patients are usually lost to follow-up. More information is needed on intra-individual changes and the proportion of patients who experience a clinically relevant change.

Moreover, the instruments chosen for the study might not have been sufficiently sensitive to tap LVAD-related changes in health status, if present.[37] Some instruments, such as the KCCQ, have also not been used optimally, since authors did not report subdomain scores. Finally, studies failed to examine key predictors of intra-individual changes in PROs over time or associations between PROs and other outcomes, such as mortality and number of hospitalizations

The need for assessing patient reported outcomes in LVAD patients

The importance of studying PROs, such as health status, is gaining increasing recognition because of the belief that an illness, its treatment, and complications affect all domains of a patient's life, and that the patient perspective is as valid as that of the clinician when it comes to evaluating outcomes.[40] In addition, information on PROs is important for future patients and families who have to make an informed decision regarding the option for LVAD therapy. Information on PROs cannot be extracted from patients' medical records or a proxy and, therefore, PROs need to be assessed in their own right. Thus, PROs may provide important additional information to health care providers and serve as targets for intervention in individual patients.[8, 9] Despite their importance, there is often a minor emphasis placed on PROs, and they are rarely included as primary outcomes in clinical LVAD trials.[6] In particular studies on continuous-flow LVADs show a tendency to neglect anxiety and depression. This is surprising given that 15%-36% of heart failure patients are known to

suffer from depression,[41, 42] 40% from anxiety,[16] and 10%-17% from posttraumatic stress disorder.[43,44] Symptoms of depression and anxiety can be disabling,[15] and are associated with an increased risk of declines in physical health,[16] mortality, higher medication costs,[15] non-compliance with treatment, malignancies,[45, 46] and hospital readmissions.[8] The limited available evidence suggests that there may be a link between LVAD technology and the patient's psychological adjustment.[5]

Recommendations for future research and care of LVAD patients

Because it has been widely established that LVAD therapy is capable of enhancing the survival of patients with end-stage heart failure, measuring PROs (e.g. functional status, quality of life and psychological distress) in these patients deserves a priority similar to survival in future LVAD studies. This review indicates that PROs improve over time, yet it also uncovers major shortcomings in their assessment, reflecting a considerable knowledge gap in the optimal care for these patients. More specific recommendations for future research and clinical practice in LVAD therapy are given in **Table 4**.

In addition to the current inter-individual approach (comparing changes in mean group scores over time), PROs should also be analyzed using an intra-individual approach focusing on the proportion of patients who experience a clinical improvement or deterioration over time. Eventually, this will create the possibility to risk stratify patients and enhancing optimal clinical practice. Attention should also be given to the selection of PRO measures, with a distinct preference for disease-specific measures such as the KCCQ or MLHFQ. Patients are more likely to identify themselves in these instruments, thereby increasing the response rate. In studies on continuous-flow devices health status was predominantly measured with the KCCQ or the MLHFQ, with both measures showing similar results in various large-scale LVAD studies.[18, 22, 23, 25, 27] This suggests that these measures are sensitive to detect LVAD-related changes in health status over time, if present. To capture psychological morbidity in LVAD patients, the Heart Failure Symptom Checklist or LVAD Stressor Scale could be used in addition to specific anxiety/depression measures. Given the paucity of studies on psychological functioning in LVAD patients, it is difficult to recommend a specific instrument to use. The Patient Health Questionnaire (PHQ-9) and the Generalized Anxiety Disorder Scale (GAD-7) might be a way to start, because both instruments have

excellent psychometric properties. In addition, these measures are exempt from copyright and can be used free of charge.

It is paramount that future studies comply with the Consolidated Standards of Reporting Trials [CONSORT] and the Strengthening the Reporting of OBservational studies in Epidemiology [STROBE] statements for reporting results of randomized trials and observational studies.[47,48] These guidelines also stipulate reporting of missing data and clinical relevance, as has also been advocated by others.[49, 50] This is needed because, for sufficiently large trials, it is possible to have a statistically significant difference that may not be clinically meaningful.[50] In clinical practice, there needs to be a shift in LVAD rehabilitation programs from survival to also focus on coping abilities and health status of LVAD patients. These programs need to be tailored to the individual patient, and should account for the patient's level of emotional functioning.

CONCLUSION

There is a paucity of studies on the patient perspective of LVAD therapy. Initial evidence suggests an improvement in health status, anxiety and depression in the first months after LVAD implantation. However, PRO scores of LVAD patients are still lower for physical, social and emotional functioning compared to transplant recipients. To advance the field of LVAD research and to optimize the management of an increasingly growing population of LVAD patients, more well designed large-scale studies on PROs are needed. By these studies, we will be able to further elucidate the psychological and social impact of LVAD therapy, thereby creating the opportunity to not only improve the care for patients after LVAD implantation, but also to provide important information that is needed by patients and families for effective decision-making regarding whether LVAD implantation is aligned with their own preferences and goals.

Table 1: Impact of LVAD therapy on patient reported outcomes - pulsatile devices (7 studies)

Author	Subtype of LVAD	N (LVAD)	N (other)	Study design*	Measure	Main findings	% of patients with clinically meaningful improvement
Health status							
Dew et al. (1999) [32]	Heartmate TCI/ Novacor	2/8	55 OMT/ 97 HTx	P (2 mo)	SIP	Improvement in physical and social functioning (not all domains significant)	Not reported
Rose et al. (2001)[†] [24, 26, 28]	Heartmate VE	68	61 OMT	P (RCT) (1 y)	SF-36, MLHFQ[3]	Significant improvement in health status	Not reported
Grady et al. (2004)[†] [10-14, 21]	Heartmate IP/VE	78	-	P (1 y)	QLI, SIP	Total QoL (psychological/ health functioning) and functional disability better for HTx compared to LVAD, psychological stressors very important in LVAD patients. No significant improvement in total QoL scores over time	Not reported
Laoutaris et al. (2010)[33]	EXCOR	15	-	P (RCT) (10 wk)	MLHFQ[3]	Training group (TG) significantly better health status after 10 weeks, no difference in control group (CG)	Not reported
Anxiety/ Depression							
Shapiro et al. (1997)[31]	Heartmate IP/VE	30	-	C	MMSE	Significant decrease in depression after 1 year	Not reported
Dew et al. (1999) [32]	Heartmate TCI/ Novacor	2/8	55 OMT /97 HTx	P (2 mo)	SLC-90	Depressive and anxiety symptoms significantly reduced over time	Not reported
Dew et al. (2000) [30]	HeartmateVE/ Novacor	19/18	-	C (1 mo)	SLC-90	Depression and anxiety significantly correlated to LVAD noise, malfunction and infection	Not reported
Rose et al. (2001)[24, 26, 28]	Heartmate VE	68	61 OMT	P (1 y)	BDI	Improved depression scores at follow-up, significantly better depression scores compared to OMT	Not reported
Baba et al. (2006) [29]	Heartmate VE/ Toyobo	13/1	-	C	Diagnostic interview	50% of patients one or more DSM-IV diagnosis	Not reported

**C= cross-sectional; P=prospective; R=retrospective; [3]D=disease specific instrument; [†]multiple studies on the same study sample; OMT= optimal medical treatment; HTX= transplant recipients. SIP= Sickness Impact Profile, MLHFQ= Minnesota Living with Heart Failure Questionnaire, QLI= Quality of Life Inde[v] SCL-90= Symptom Checklist-90, MMSE= Mini-Mental State Exam*

Table 2: Impact of LVAD therapy on patient reported outcomes - continuous-flow devices (9 studies)

Author	Subtype of LVAD	N (LVAD)	N (other)	Study design	Measure	Main findings	% of patients with clinically meaningful improvement
Health status							
Siegenthaler et al. (2005) [38]	Jarvik 2000	17	-	P (3 mo)	MLHFQ[1]	Health status significantly improved	Not reported
Slaugther et al. (2009)[27]	HeartmateVE/ Heartmate II	66/134	-	P (2 y)	MLHFQ[1], KCCQ[1]	Health status improved significantly. No significant difference between pulsatile and continuous devices for MLHFQ	Not reported
Allen et al. (2010)[36]	HeartmateVE/ Heartmate II	7/23	-	R	MLHFQ[1]	Health status scores correlate to NYHA I-II	Not reported
Rogers et al. (2010)[2] [18, 22, 23, 25, 27]	Heartmate II	655	-	P (2 y)	MLHFQ[1], KCCQ[1]	Health status significantly improved	79% BTT, 92% DT patients
Kugler et al. (2010)[37]	Heartmate II	36	54 HTx	P (6 mo)	SF-36	No significant improvement in LVAD group over time, HTx group significantly better physical functioning and mental health	Not reported
Meyer et al. (2010)[35]	Heartmate II/ HVAD	17/10	-	C	SF-36	Half of health status domains significantly lower for LVAD compared to general population	Not reported
Bogaev et al. (2011) [4 18, 22, 23, 25, 27]	Heartmate II	465	-	P (6 mo)	MLHFQ[1], KCCQ[3]	Health status scores improved significantly. No gender difference in health status scores.	Not reported
Starling et al. (2011)[39]	HeartmateVE/ II Thoratec pVAD	338	-	P (1 y)	EuroQol EQ-5D	QoL significantly improved at 12 months after LVAD support	Not reported
Anxiety/Depression							
Bunzel et al. (2007)[4 19, 20]	Novacor LVAS/ Thoratec pVAD/ DeBakey VAD/ Duraheart	8/17 /4/9	27 partners	C	IES-R, HADS	No significant impact	Not reported

C= cross-sectional; P=prospective; R=retrospective; [1]D=disease specific instrument; [2]multiple studies on same study sample; HTX= transplant recipients; DT=destination therapy; BTT=bridge-to-transplantation. MLHFQ= Minnesota Living with Heart Failure Questionnaire, KCCQ= Kansas City Cardiomyopathy Questionnaire, HADS= Hospital Anxiety and Depression Scale, IES-R= Impact of Event Scale-Revised

Table 3: Overview of sample size, follow-up and missing data of LVAD studies with health status assessments

Author	N (other)	Max. PRO follow-up reported*	Number of LVAD study patients alive over time (N)									
			Baseline	2 mo	3 mo	6 mo	1 year	2 years	Mean % of living patients having PRO data *overall*	% of living patients having PRO data at *end of follow-up*	Reason for missing data at inclusion and follow-up	Information on handling of missing data
Pulsatile devices												
Dew et al. (1999) [32]	55 OMT /97 HTx	P (2 mo)	10	10	-	-	-	-	All patients	All patients	HTx, too ill, refused or language issue	No
Rose et al. (2001) [4, 24, 26,28]	61 OMT	P (RCT) (1 y)	68	-	-	38	24	5	92%	92%	Deceased, too ill or no transportation	No
Grady et al.(2004)† [10-14, 21]	-	P (1 y)	78	-	43	-	9	-	All patients	All patients	HTx, too ill, refused deceased	No
Laoutaris et al.(2010) [25]	-	P (RCT) (10wk)	15	15	-	-	-	-	All patients	All patients	-	No
Continuous flow devices												
Siegenthaler et al. (2005) [38]	-	P (3 mo)	17	-	-	11	7	4	61.3%	75.0%	Deceased	Yes
Slaugther et al. (2009) [4 18, 22, 23, 25, 27]	-	P (2 y)	200	-	-	127	101	64	77.6%	60.5%	Deceased, HTx	No
Rogers et al. (2010) [4 18, 22, 23, 25, 27]	-	P (2 y)	655	-	460	380	213 (only DT)	101 (only DT)	82.5% BTT, 90.7% DT	82.8% BTT, 88.5% DT	Deceased, HTx, staff availability	No
Kugler et al. (2010) [37]	54 HTx	P (6 mo)	36	-	-	34	-	-	75.0%	64.3%	Deceased, refused, drop-out	Yes

Bogaev et al. (2011)[4] [18, 22, 23, 25, 27]	-	P (6 mo)	465	-	-	251	150	121 (18 mo)	79.5%	85.1%	Deceased, HTx, staff availability	Yes
Starling et al. (2011)[39]	-	P (1 y)	338	-	306	196	128	-	46.1%	48.4%	Not reported	No

**C= cross-sectional; P=prospective; R=retrospective; [3]D=disease specific instrument; G=generic instrument; [†]multiple studies on the same study sample, DT= destination therapy, HTX= heart transplantation*

Table 4: Recommendations for the incorporation of PRO assessments in clinical practice and future research

	CLINICAL PRACTICE	FUTURE RESEARCH
Purpose of incorporating PROs in clinical practice and research	• PROs have unique prognostic value above and beyond physician-rated measures and information derived from patients' medical status • Inclusion of the patient perspective; no proxy measure available from measures assessed in standard clinical setting • PROs may facilitate communication between patients and physicians • PROs may enhance identification of high-risk patients whose medical treatment should be optimized • PROs can be used as performance measures to evaluate the quality of care	• Evaluate the impact of treatment, devices and device settings on PROs using both health status and anxiety/depression measures • Comparison of PROs between LVAD patients and other groups (e.g. patients on optimal medical treatment, HTx) is necessary for informed political and clinical decision-making • Compare the sensitivity of disease-specific and generic PRO measures to detect changes over time; if necessary develop new disease-specific measures e.g. to assess anxiety and depression
Recommendations for PROs as primary outcomes in LVAD research and therapy	• Enables more accurate tracking of changes in patient's physical and psychological functioning over time, and better coordination of care (e.g. individually tailored rehabilitation programs) • Is a no-risk, low-cost and low-burden addition to clinical care	• Examine the correlation between clinical variables and PROs and determine their relative importance for LVAD patient prognosis • Use both an inter- and intra-individual approach in data analyses • Adhere to *CONSORT and STROBE statement* guidelines for reporting critical PRO data elements (e.g. missing data and clinical meaningful improvement) • Use of disease specific questionnaires (e.g. MLHFQ, KCCQ) in studies with LVAD cohorts only • Incorporate PRO instruments for anxiety and depression in studies on continuous-flow devices • Use prospective studies with large sample sizes

QoL= quality of life, PROs= patient reported outcomes

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CHAPTER 3

Psychological distress in patients with a left ventricular assist device and their partners: An exploratory study

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ABSTRACT

Background: Left ventricular assist device (LVAD) therapy is increasingly used in patients with advanced heart failure, and may have a significant psychological impact on both patients and their partners. Hence, we examined the distress levels of LVAD patients and their partners.

Methods: Anxiety, depression and post-traumatic stress (PTSD) were assessed at 3-4 weeks after implantation, and at 3 and 6 months follow-up in 33 LVAD patients (73% men; mean age=54±10years) and 33 partners (27% men; mean age=54±11 years).

Results: The prevalence of anxiety in LVAD partners was significantly higher compared to LVAD patients at baseline (48% vs. 23%, p=.03) and 3 months (44% vs. 15%, p=.02), but not at 6 months follow-up (p=.43). No differences were found for depression and PTSD (ps>.05). Scores between the LVAD patients and partners showed only a significant correlation at baseline for the anxiety, depression and PTSD score of the patient and the depression score of the partner (r_{anx}=.40, p=.04; r_{dep}=.40, p=.04; r_{PSTD}=.46, p=.05). Multivariate analyses showed no significant association between the role (patient vs. partner) and anxiety, depression and PTSD over time after correction for age, gender and clinical covariates. However, after correction for Type D personality and the use of psychotropic medication the LVAD partners showed significantly higher anxiety (F=6.95, p=.01) and depression (F=3.94, p=.04) scores over time compared to LVAD patients.

Conclusion: LVAD partners had significantly higher levels of anxiety than LVAD patients. Emotional distress of LVAD partners should gain more attention, as partners are an essential source of support for LVAD patients.

INTRODUCTION

As donor hearts for transplantation continue to be extremely limited, the left ventricular assist device (LVAD) is becoming an indispensible tool for patients with advanced heart failure whose medical treatment options have been exhausted.[1,2] With the increasing availability of the new generation axial and centrifugal pumps, the incidence of morbidity and mortality is decreasing and LVADs are becoming more patient friendly with respect to size and durability.[1, 3] Despite these advances, LVAD therapy is a complex treatment with a trajectory that is often marked by intense physical rehabilitation, complications, frequent hospitalization and social isolation.[4,5] As a consequence, quality of life has become an important complementary end-point in large clinical trials in addition to morbidity and mortality in this patient population.[6, 7]

While the evidence on quality of life of LVAD patients continues to grow, this is not the case for evidence on psychological distress (e.g. anxiety and depression), which has only been adequately assessed in older studies during the era of pulsatile devices.[8] This is surprising given that 15%-36% of patients with heart failure patients experience depression, 40% anxiety,[9] and 10%-17% posttraumatic stress disorder.[10,11] Moreover, although the awareness of the partner's and the family's role in the patient's adaptation to cardiovascular disease is increasing, only a few studies focused on the emotional well-being of partners and caregivers of LVAD patients.[12-14,44-45] These studies found that LVAD partners experienced a greater caregiver burden in comparison to partners of heart transplant recipients, and that psychological distress of LVAD partners was mostly related to fear of stroke, device malfunction and infection.[13] Studies on patients with heart failure and their partners show that partner levels of psychological distress are often on par with patient levels.[15-17] Patients tend to score lower on physical health status as compared to their partners, but not always on mental health status.[5,7,16,18] Furthermore, patients and partners score lower on mental health compared to the general population.[4,15, 19] The level of psychological distress in heart failure patients and partners may be influenced by age, gender, disease severity and personality (i.e. Type D personality).[15,16,20] However, it is unknown whether these same factors could play a role in the psychological distress levels of patients after LVAD therapy.

Therefore, this study examined the prevalence of psychological distress (anxiety, depression and post-traumatic stress) in LVAD patients and their partners and compared the scores on psychological distress over time in patient-partner dyads.

METHODS

Study population and design

This paper reports on a multi-center prospective observational study in which adults with advanced heart failure implanted with the axial-flow HeartMate II LVAD (Thoratec) or centrifugal-flow HVAD (HeartWare) as a bridge-to-transplant were eligible for study participation. Patients were recruited as a consecutively implanted cohort from the University Medical Center, Utrecht and the Erasmus Medical Center, Rotterdam, the Netherlands and the Heart Center at St. Paul's hospital in Vancouver, Canada, between January 2011 and February 2013. Patients were eligible for inclusion if they had not undergone a previous LVAD implantation, were ≥18 years of age, were proficient in the Dutch or English language and had no history of severe psychiatric illness other than cognitive-affective disorders. Partners could consent to participate in the study only if the LVAD patients had consented to participate.

Patients and partners were asked to complete a set of standardized and validated questionnaires at baseline (i.e. 3-4 weeks after LVAD implantation) and at 3 and 6 months follow-up. The baseline assessment was performed when patients were given the LVAD-training while still being hospitalized, indicating that they had recovered sufficiently for study participation. The follow-up assessments were sent out by mail around the same time points as the visits to the outpatient clinic. The questionnaires were returned in a stamped, pre-addressed envelope. If the questionnaire was not returned within two weeks, patients and partners received a reminder telephone call or letter. The study was approved by the Medical Ethics Committee of the participating hospitals, and conducted in accordance with the Helsinki Declaration (2008).

Measures

Demographic and clinical variables

Information on demographic variables comprised sex, age, marital status, and educational level and were collected both on patients and partners. Clinical variables for patients and partners included body mass index (BMI), medical comorbidity and use of psychotropic medication. Information on these demographic and clinical variables was extracted from purpose-designed questions in the questionnaires and from the patients' medical records. A comorbidity score was computed using the Charlson Comorbidity Index (CCI), which

evaluates 17 different comorbidities with varying assigned weights. We used an abbreviated CCI score with the following comorbid conditions: myocardial infarction (MI), cerebrovascular disease, chronic obstructive pulmonary disease, diabetes mellitus, peripheral vascular disease, liver disease, renal failure, and any malignancy excluding metastatic tumors.[21]

Other clinical variables for the patients included duration of hospitalization, etiology, left ventricular ejection fraction (LVEF), New York Heart Association (NYHA) functional class, prescribed medications (i.e., beta-blockers, aldosterone receptor antagonists, anticoagulants, ACE-inhibitors, statins and diuretics), previous cardiac events (i.e., myocardial infarction, coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI)) and the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) score. The INTERMACS score was developed by the INTERMACS Coordinator's Council as a result of the existing limitations for clinical characterization of mechanical circulatory support recipients. It is a valid score system that is increasingly used as a tool to assess the patient's profile and predicts complications and mortality after LVAD implantation. Seven profiles have been defined for the INTERMACS registry ranging from *crash-and-burn* patients (INTERMACS 1) to patients with advanced NYHA III (INTERMACS 7).[22-24]

Symptoms of anxiety and depression

The 14-item Hospital Anxiety and Depression Scale (HADS) was used to assess symptoms of depression and anxiety.[25-27] Items are answered on a four-point Likert Scale from 0-3 (range [0-21]). The HADS is a valid and reliable measure, which has strong psychometric properties[25,26] and has shown to be an adequate measure of anxiety and depressive symptoms in cardiac patients.[28] We used a cut-off of ≥8 to indicate the presence of symptoms of anxiety and depression, based on the optimal cut-off found in large-scale studies.[29]

Post-traumatic stress disorder

Symptoms of post-traumatic stress (PTSD) were assessed with the Posttraumatic Stress Diagnostic Scale,[30] a 17-item self-report instrument that can be used to generate a diagnosis that is consistent with the diagnostic criteria for post-traumatic stress.[31] To ensure that post-traumatic stress was related to the LVAD implantation and not to other traumatic events,

patients were asked to rate each item according to the 'LVAD implantation'. A similar approach has been used by others.[32] To qualify for a diagnosis of post-traumatic stress, the respondent has to endorse at least: 1 re-experiencing symptom, 3 avoidance symptoms, and 2 hyperarousal symptoms. Items are rated on a 4-point scale ranging from 0 (*not at all*) to 3 (*almost always*). It is also possible to calculate a total PTSD symptom score by summing up the 17 items. The scale has good sensitivity and specificity with a high internal consistency (Cronbach's $\alpha = .92$) and test–retest reliability for a PTSD diagnosis ($\kappa = .74$).[30]

Type D personality

The Type D Scale (DS14) was used to assess the distressed (Type D) personality defined by a cut-off of ≥10 on both negative affectivity and social inhibition.[33,34] Negative affectivity refers to the tendency to experience negative emotions, like anger, dysphoria and irritability. Social inhibition refers to discomfort in social interactions, reticence and lack of social poise. The negative affectivity and social inhibition scales showed to be internally consistent (alpha= 0.88/0.86) and stable over a 3-month period (test-retest r= 0.72/0.82). Items are rated on a 5-point Likert scale. The construct of Type D personality is stable when compared to the effect of gender on outcomes. The DS14 was administered at baseline.

Statistical analyses

The χ^2-square test was used to examine differences on discrete variables and Student's t-test for independent samples to examine differences on continuous variables. The correlations between the continuous anxiety, depression and PTSD scores between LVAD patients and partner were calculated using Pearson's correlation coefficient. For the multivariate analyses, we used the linear mixed model procedure (covariance model: *compound symmetry*, maximum likelihood (ML) estimate) in SPSS version 19.0, which is comparable to a linear regression analysis except for the fact that the dependent variable is measured at multiple occasions over time. The mixed model procedure uses all the available time points available for each patient and partner, thereby limiting bias and preserving statistical power. The dependent variables included in this analysis were the continuous scores on anxiety, depression and PTSD at baseline, 3 months and 6 months. First, role (patient vs. partner), gender, age and time were entered into the model. By entering these variables we examine whether the mean scores of anxiety, depression and PTSD were significantly different for

patients and partner, whether the scores changed significantly between baseline and 6 months and whether differences between patients and partners were due to age and gender. In an additional model, we also added clinical variables (i.e. the length of hospitalization from baseline until discharge (in days), INTERMACS score, comorbidity) and psychosocial variables (Type D personality, use of psychotropic medication).

RESULTS

Of the 90 patients who met the inclusion criteria from all three centers, 20 patients refused participation, 16 patients died or were too ill at the time of inclusion and 3 were excluded due to inability to write and read English, low intellectual functioning or because they had a LVAD replacement, leaving a sample of 51 patients for analyses. The patients not participating in the study did not differ systematically on age, gender and type of LVAD compared to patients who participated ($p>.05$).

Subsequently, the partners of these patients were asked to participate in the study. As this study was only focused on the psychological distress in LVAD patients and their partners, only the patients whose partner also participated in the study were used in the analyses. Eighteen partners refused participation leaving 33 patient partner dyads for analyses. Of the 33 LVAD patient-partner dyads, n=27 were included in the Netherlands and n=6 in Canada.

Patient and partner characteristics

Baseline characteristics stratified by LVAD patient versus partner status are presented in **Table 1**. Patients were more likely to be male (73% vs. 27%; $p<.001$), to have more co-morbidities ($p=.005$), and to have a Type D personality (27% vs. 6%; $p=.02$). Further clinical information on LVAD patients is given in **Table 2**.

There was a significant difference in the prevalence of anxiety between patients and partners at baseline (23% vs. 48%, $p=.03$) and 3 months follow-up (15% vs. 44%, $p=.02$) but not at 6 months follow-up (15% vs. 26%, $p=.43$). There was no significant difference between patients and partners in the prevalence of depression (28% and 39%, $p=.37$) and post-traumatic stress (21% v. 12%, $p=.32$) at baseline, 3 months follow-up (23% vs. 32%, $p_{depr}=.48$; 21% and 12%; $p_{PTSD}=.32$) and 6 months follow-up (5% vs. 23%, $p_{depr}=.15$; 9% vs. 14%, $P_{PTSD}=.69$).

Patients using psychotropic medication (n=13) were more likely to have post-traumatic stress at baseline than patients not using psychotropic medication (n=9) (χ^2=3.82, p=.05; *data not shown*). There was no difference in the prevalence of anxiety, depression or post-traumatic stress in the partners who used (n=6) or did not use (n=23) psychotropic medication, except for a higher prevalence of anxiety at 3 months follow-up for patients using psychotropic medication (n=6) (χ^2=5.38, p=.02; *data not shown*).

Table 1: Baseline characteristics of LVAD patients and partners (n=33) *

	LVAD Patients (n= 33) Mean±SD N (%)	**LVAD Partners (n=33)** Mean±SD N (%)	**p-value**
Demographics			
Male	24 (73)	9 (27)	**<.001**
Age (yrs), mean (SD)	54.7±10.6	53.6±10.7	.67
Higher education[1]	29 (88)	31 (94)	.39
Employed	14 (42)	24 (73)	**.01**
Clinical			
Comorbidity Index[2]			**.005**
0	0 (0)	8 (24)	
1	10 (30)	15 (46)	
2	9 (27)	7 (21)	
3	10 (30)	1 (3)	
4	2 (6)	2 (6)	
≥5	2 (6)	0 (0)	
BMI, mean (SD)	28.5±21.1	25.9±4.8	.50
Psychotropic medication			
Anti-depressants	1 (3)	1 (3)	.98
Anxiolytics	5 (15)	3 (9)	.48
Sleep medication	9 (27)	4 (13)	.14
Type D personality[3]	9 (27)	2 (6)	**.02**

**Results are reported as n (%) unless otherwise indicated*

[1]Higher education= secondary school and above; [2]Comorbidity index= comorbidity was calculated using the abbreviated Charlson Comorbidity Index; [3]Based on the standardized cut-off value of ≥10

Table 2: Clinical characteristics of LVAD patients at baseline (n=33)

	LVAD patients (n=33) Mean±SD; N (%)
Clinical	
Type of LVAD	
HeartMate II	22 (67)
HeartWare	11 (33)
Length of hospitalization stay (in days)	48.5±27.4
INTERMACS gradation	
1	5 (15)
2	12 (36)
3	11 (34)
4	5 (15)
Etiology	
Ischemic	15 (45)
Dilated cardiomyopathy	13 (40)
Other (hypertrophic, myocarditis)	5 (15)
Previous CABG	5 (15)
Previous PCI	11 (35)
Previous valve replacement	2 (6)
Previous myocardial infarction	13 (40)
Previous ICD/CRT-D implantation	24 (73)
Previous CVA	5 (15)
LVEF	18.5±7.8
IABP	4 (12)
ECMO	3 (9)
Cardiac medication	
Amiodarone	21 (65)
Beta-blockers	17 (53)
Angiotensin-converting enzyme inhibitors	22 (69)
Statins	15 (47)
Inotropics	22 (70)
Coumarin (derivates)	33 (100)

CABG= coronary artery bypass graft; PCI=percutaneous coronary intervention; ICD= implantable cardioverter defibrillator; CRT-D= cardiac resynchronization therapy; CVA= cerebrovascular accident; NYHA= New York Heart Assocation; LVEF= left ventricular ejection fraction; IABP= intra-aortic balloon pump; ECMO=extracorporeal membrane oxygenation; INTERMACS= Interagency Registry for Mechanically Assisted Circulatory Support

Correlation between psychological distress at baseline, 3 and 6 months in LVAD patients and partners

Table 3 shows that patients' and partners' own psychological distress scores were strongly correlated at baseline, and at 3 and 6 months follow-up ($p<.05$). Scores between the LVAD patients and partners showed only a significant correlation at baseline for the anxiety, depression and PTSD score of the patient and the depression score of the partner ($r_{anx}=.40$, $p=.04$; $r_{dep}=.40$, $p=.04$; $r_{PSTD}=.46$, $p=.05$).

Psychological distress from baseline to 6 months follow-up in LVAD patients and partners

Using mixed multivariate modeling, the average level of anxiety, depression and PTSD over time was examined for LVAD patients and partners **(Table 4)**. Being a patient or partner was not significantly associated with higher anxiety ($F=3.00$, $p=.08$), depression ($F=.55$, $p=.47$) or PTSD ($F=.01$, $p=.92$) scores after correction for age and gender **(Figure 1)**. Additional correction for comorbidity, INTERMACS gradation and duration of hospitalization did not alter these findings (anxiety, $F=2.71$ $p=.11$; depression, $F=.66$ $p=.42$; PTSD, $F=.01$, $p=.93$). However, after adding Type D personality and the use of psychotropic medication to the model, LVAD partners showed a significantly higher score on anxiety ($F=6.95$, $p=.01$) and depression ($F=3.94$, $p=.04$) as compared to LVAD patients. The averaged level of anxiety, depression and PTSD decreased significantly over time between baseline and 6 months in both LVAD patients and their partners ($p<.01$ for all). Patients and partners with a Type D personality showed significantly higher levels of anxiety ($F=7.48$, $p=.008$), depression ($F=5.40$, $p=.02$) and PTSD ($F=19.45$, $p<.001$) over time. Age, gender, duration of hospitalization, INTERMACS gradation and use of psychotropic medication were not significantly correlated with anxiety, depression and PTSD of LVAD patients and their partners over time.

DISCUSSION

The results of this study indicate that partners of LVAD patients may fare worse than LVAD patients with respect to psychological distress. At baseline, partners were more likely to be anxious than patients, and there was a trend towards a higher prevalence of depression. Comparing the outcomes of LVAD patients in our study to former studies is not straightforward given that majority of studies on psychological distress in LVAD patients have been based on the first generation of LVADs,[35] used different assessment scales[13, 36-38]

or were retrospective.[14] The REMATCH trial, and other more recent studies, found that depression and anxiety are prevalent in LVAD patients shortly after implantation, with prevalence rates ranging between 21-50%.[36-39] These relatively high prevalence rates may be attributed to the challenges that patients face particularly shortly after implantation, such as complications, cardiac rehabilitation and medication-, driveline-, and device-training, which could make them vulnerable to distress. The prevalence of distress seems to decrease rapidly over the next 6 months, indicating that anxiety and depressive symptoms remit in the majority of LVAD patients following discharge from hospital. Studies on PTSD in LVAD patients are scarce, but studies in general cardiovascular patients show a prevalence of PTSD ranging between 0-22% in patients post MI, 1-15% in heart transplant recipients and up to 24% in patients undergoing cardiac surgery.[40-43] The latter prevalence is in line with our findings in LVAD patients.

There are only a few studies examining the psychological distress in LVAD patients and their partner, most of which have a qualitative study design.[12, 39, 44, 45] One study of Bunzel et al., which uses a retrospective study design, found a higher prevalence of anxiety (23% vs. 4%), depression (19% vs. 2%) and PTSD (26% vs. 0%) in LVAD partners as compared to patients.[14, 46] Although our study also found a higher prevalence of anxiety and depression in partners, there is a large discrepancy in the prevalence found in our sample as compared to those found by Bunzel et al. This large difference could be explained by the fact that those patients underwent LVAD implantation on average 6 years prior to assessment and were at that time already transplanted, thereby making it difficult to distinguish if their anxiety, depression and PTSD were LVAD or heart transplant-related. Most other studies on psychological distress in heart failure patients and their spouses found no significant differences[15, 16, 47] or found that patients had significantly higher depression scores[5, 7, 18] and a higher prevalence of PTSD than partners (10.5% vs. 7.7%).[48] Differences in the findings of these studies and our findings suggest the psychological distress of partners might be LVAD-specific and less related to the heart failure of the patient.[12,39] Former studies found that psychological distress in LVAD partners originates from fear of the LVAD itself, of living with the LVAD and the knowledge and skills they need to obtain to become a good caregiver, but also from fear of complications.[12, 39, 49] Yet, it seems that most partners find a way to accept and cope with all the changes, and to gain a positive view on the future over the next few

months after implantation,[45] which may explain the decrease in anxiety, depression and post-traumatic stress scores among the partners in our sample.

Table 3: Correlations between anxiety, depression and PTSD scores in LVAD patients and their partners*

Baseline	**1**	**2**	**3**	**4**	**5**
1. Patient - Anxiety	-				
2. Patient - Depression	**.76*** **	-			
3. Patient - PTSD	**.76*** **	**.65*** **	-		
4. Partner - Anxiety	**.33**	**.28**	**.36**	-	
5. Partner - Depression	**.40***	**.40***	**.46***	**.72*** **	-
6. Partner - PTSD	**.27**	**.28**	**.26**	**.85*** **	**.73*** **
3 months follow-up					
1. Patient - Anxiety	-				
2. Patient - Depression	**.53*** **	-			
3. Patient - PTSD	**.79*** **	**.68*** **	-		
4. Partner - Anxiety	**.36**	**.04**	**.11**	-	
5. Partner - Depression	**.31**	**.07**	**.07**	**.42***	-
6. Partner - PTSD	**.10**	**-.23**	**-.03**	**.68*** **	**.65*** **
6 months follow-up					
1. Patient - Anxiety	-				
2. Patient - Depression	**.56*** **	-			
3. Patient - PTSD	**.78*** **	**.81*** **	-		
4. Partner - Anxiety	**.07**	**-.11**	**-.10**	-	
5. Partner - Depression	**.02**	**-.01**	**-.01**	**.71*** **	-
6. Partner - PTSD	**.01**	**-.10**	**-.01**	**.81*** **	**85*** **

***p <.05; ***p<.01*

Interestingly, correlational analyses showed that the anxiety, depression and PTSD scores in LVAD patients and partners were not strongly related to one another, especially at 3 and 6 months follow-up. One other study also found a significant correlation between the depression scores of heart failure patients and their partners,[16] however not among younger patients and partners, while other studies found no correlation at all.[5,15] Based on the

findings of the multivariate analyses, LVAD partners were more prone to experience symptoms of anxiety than LVAD patients. Furthermore, having a Type D personality significantly increased the likelihood of psychological distress in LVAD patients and partners, as was also found by Romppel et al.[49] and Pedersen et al.[50] in cardiac and MI patients.

SUMMARY

Overall, this is the first study examining the psychological distress in LVAD patients and their partner using a quantitative longitudinal study design. Our findings underscore the need for continued research on psychological distress in LVAD patients and their partners in order to provide effective counseling and support, prevent long-term psychological morbidity and improve the lives of LVAD patient-partner dyads. Although we found a decrease in distress in LVAD patients and partners from baseline to 3 months, some LVAD patients and partners might experience chronic symptoms that persist over time. As it is known from other cardiovascular populations that anxiety, depression and PTSD can increase the risk for adverse clinical outcomes[51] including mortality,[10,52,53] it is important to examine whether patients scoring high on distress at baseline are really recovering and whether it is baseline distress, chronic distress or new onset distress that incurs the greatest risk for poor prognosis.

Limitations

The limitations of this study should be acknowledged and include the relatively small sample size and number of female LVAD patients. Therefore, it was not possible to stratify our results for gender, age, use of psychotropic medication or site. As the clinical and psychological care of LVAD patients might slightly differ between the centers this could have impinged on the results. Patients and partners who refused study participation might have suffered from more psychological distress, therefore the results on anxiety, depression and PTSD in this paper could be an underestimation of the actual situation. Furthermore, this was a prospective study with a short-term (i.e. 6 months) follow-up, warranting replication of these findings over a longer period of time. The absence of information on demographic and clinical characteristics of the Canadian LVAD patients that did not participate might have a negative effect on the external validity of this study. We used self-report measures of psychological distress rather than a clinical diagnostic interview. However, also minimal

symptoms of distress assessed with a self-report measure have been shown to predict morbidity and mortality in cardiac patients.[54]

Implications for practice

- As distress in partners may influence patients' psychological adjustment, treatment adherence and even mortality,[55] it would be important to assess and monitor distress in partners and to provide extra attention, education or support to partners if necessary.
- Furthermore, more research is required on patient-partner dyads in relation to LVAD therapy in order to identify the specific problems and needs that might enhance the quality of care and outcomes after LVAD therapy.

Table 4: Mixed modeling of anxiety, depression and PTSD scores over time (baseline - 6 months) in LVAD patients and their partners

	Anxiety	Depression	PTSD
Model 1			
Patient vs. partner	O	O	O
Older age	O	O	O
Male gender	O	O	O
Model 2			
Patient vs. partner	O	O	O
Older age	O	-	O
Male gender	O	O	O
Comorbidity	O	O	O
INTERMACS	O	O	O
Duration hospitalization	O	O	O
Model 3			
Patient vs. partner	--	--	O
Older age	O	O	O
Male gender	O	O	O
Type D personality	+++	++	+++
Psychotropic medication	O	O	O

O= no association, p >.10

−− = negative association, p <.05; −−− = negative association, p<.01

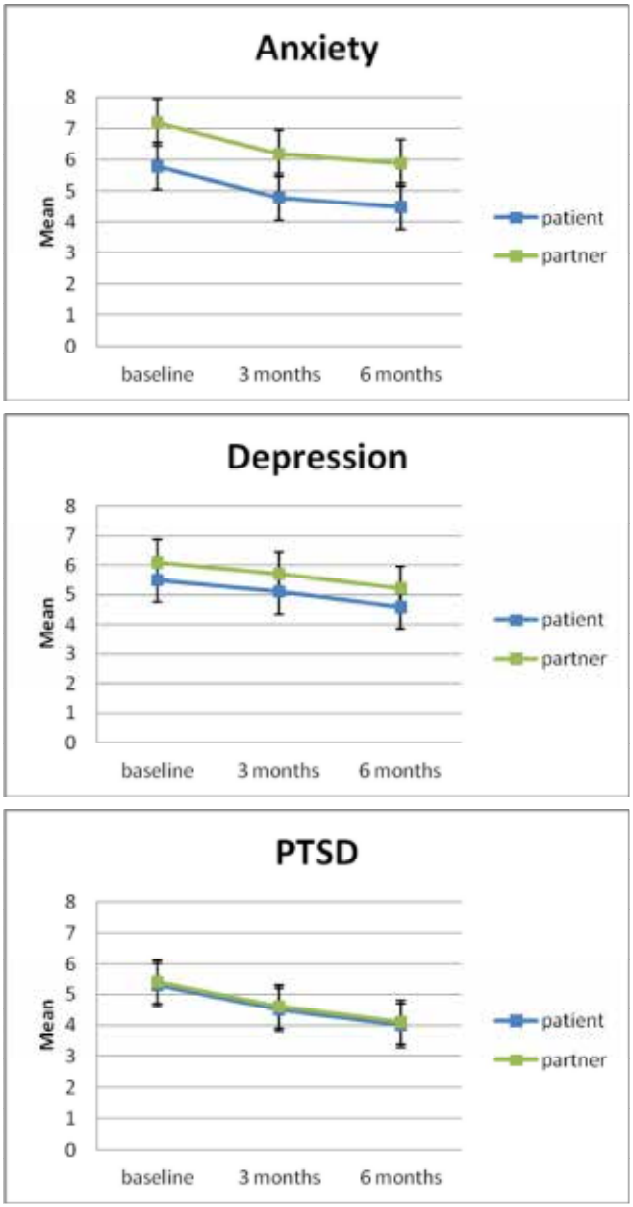
++ = positive association, p < .05; +++ = positive association. P < .01

Model 1: role (patient vs. partner) age, gender, time

Model 2: model 1 + clinical covariates (INTERMACS, duration hospitalization, comorbidity)

Model 3: model 1 + psychosocial covariates (Type D personality, psychotropic medication)

Figure 1: Mean scores (SE) of anxiety, depression and PTSD for patients and partner from baseline to 6 months follow-up*



**No significant differences in patients and partners over time (anxiety, F=2.62, p=.11; depression, F=.55, p=.47; PTSD, F=.01, p=.92) scores after correction for age and gender*

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CHAPTER 4

Predictors of changes in health status between and within patients 12 months post left ventricular assist device implantation

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ABSTRACT

Background: Improving patient-reported outcomes (e.g. health status) has become an important goal in left ventricular assist device (LVAD) therapy, in addition to reducing mortality and morbidity. We examined predictors of changes in health status scores between and within patients 12 months post LVAD implantation.

Methods: Health status (Kansas City Cardiomyopathy Questionnaire (KCCQ); Short-Form 12 (SF-12)) were assessed at 3-4 weeks post implantation, and at 3, 6 and 12 months follow-up in 54 LVAD patients (74% men; mean age=54±9years).

Results: Patients experienced significant improvements in health status between baseline and 3 months follow-up as assessed by the KCCQ (Clinical Summary Score: F=33.49, *P*<.001; Overall Summary Score: F=31.13, *P*<.001) and the SF-12 (Physical Component Score: F=31.59, p<.001; Mental Component Score: F=21.77, p<.001), but not between 3 months and 12 months follow-up (p>.05 for all). Higher scores on anxiety and depression over time, older age, lower ejection fraction, and more comorbidity were associated with poorer health status scores on one or both of the KCCQ and SF-12 subscales. The majority of the between-patient variance of the MCS scores (82.6%), but not the KCCQ-OS (41.9%), KCCQ-CS (36.2%) and PCS scores (23.2%), was explained by the socio-demographic, clinical and psychological factors.

Conclusion: The majority of LVAD patients show a significant improvement in health status after LVAD implantation. However, there are large differences in individual health status score trajectories which are only partially explained by measures of disease severity pre-LVAD, comorbidity and psychological stress.

INTRODUCTION

In the last few years, left ventricular assist device (LVAD) therapy has evolved as an alternative therapy for end-stage heart failure patients who do not qualify for cardiac transplantation, or as a bridge to transplant.[1] With the introduction of the second- (axial) and third-generation (centrifugal) continuous-flow LVADs, tremendous technical improvements have been achieved leading to a lower incidence of morbidity and mortality.[2] Besides reducing mortality an important goal of LVAD therapy is the improvement in patient-reported outcomes, such as quality of life.[3] Quality of life is a multidimensional concept which encompasses subjective health status as well as social, environmental and emotional domains.[4] Questionnaires used for measuring subjective health status can be either disease-specific or generic, enabling the comparison of outcomes with other heart failure patients or across other disease groups, respectively.[5] Patient-reported outcomes can be used to assess the effectiveness of treatment, improve informed decision making, enhance the quality of care and management of patients, and to help allocate resources to patients who need it the most.[6-8] Poor patient-reported health status has also been shown to predict mortality and rehospitalization in patients with coronary artery disease and heart failure independent of traditional biomedical risk factors.[9]

The majority of studies on health status in patients with a continuous-flow LVAD show significant improvements in mean health status scores from baseline up to 3, 6 and 12 months follow-up using various instruments.[2,10-16] Differentiating the groups of LVAD patients based on age, sex or type of LVAD did not alter these findings.[11, 15, 16] However, Rogers et al. did find that the group of LVAD patients indicated for destination therapy had a higher improvement in median health status scores between baseline and 6 months compared to the group of LVAD patients indicated for bridge-to-transplant.[17] Thus far, the studies on continuous-flow LVADs, which measured health status over time as a primary or secondary outcome, often did not report on the clinically relevant change of health status nor examined the potential predictors of changes in health status over time. Furthermore, scores on health status are reported as mean scores of the patient sample rather than examining differences in individual trajectories of health status scores of time. Examining the predictors of health status scores of individual LVAD patients is important, as it may give an indication for the post-implantation course and may help determine the appropriate intensity of follow-up care.[18]

Hence, the goal of this study was to examine the predictors of the mean health status scores but also the individual health status scores of LVAD patients over time, using a disease-specific and generic instrument.

METHODS

Study population and design

Adults with advanced heart failure implanted with the axial-flow HeartMate II LVAD (Thoratec) or centrifugal-flow HVAD (HeartWare) as a bridge-to-transplant were eligible for study participation. Patients were recruited as a consecutively implanted cohort from the University Medical Center, Utrecht and the Erasmus Medical Center, Rotterdam, the Netherlands and the Heart Center at St. Paul's hospital in Vancouver, Canada, between 2011 and 2013. Patients were eligible for inclusion if it was their first LVAD implant, ≥18 years of age, proficient in the Dutch or English language and had no history of severe psychiatric illness other than cognitive-affective disorders. Study endpoints included heart transplantation or death.

Patients were asked to complete a set of standardized and validated questionnaires at baseline (i.e., 3-4 weeks after LVAD implantation when patients were still hospitalized but recovered sufficiently for study participation), and at 3, 6 and 12 months follow-up. The follow-up assessments were scheduled at the same time points as the visits to the outpatient clinic in order to minimize burden to patients. The questionnaires were returned in stamped, pre-addressed envelopes. If the questionnaire was not returned within two weeks, patients received a reminder telephone call or letter. The study was approved by the Medical Ethics Committee of the participating hospitals, and conducted in accordance with the Helsinki Declaration (2008).

Measures

Demographic and clinical variables

Information on demographic variables comprised sex, age, marital status, employment and educational level. Information on clinical variables for patients and partners included body mass index (BMI), medical comorbidity and use of psychotropic medication. Information on these demographic and clinical variables was extracted from purpose-designed questions in the questionnaires and from patients' medical records. A comorbidity score was computed

using the Charlson Comorbidity Index (CCI), which evaluates 17 different comorbidities with varying assigned weights. We used an abbreviated CCI score with the following comorbid conditions: myocardial infarction (MI), cerebrovascular disease, chronic obstructive pulmonary disease, diabetes mellitus, peripheral vascular disease, liver disease, renal failure, and any malignancy excluding metastatic tumors.[19] Other clinical variables for the patients included duration of hospitalization, etiology, left ventricular ejection fraction (LVEF), New York Heart Association (NYHA) functional class, the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) score, prescribed medications (i.e., beta-blockers, aldosterone receptor antagonists, anticoagulants, ACE-inhibitors, statins and diuretics) and previous cardiac events (i.e., myocardial infarction, coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI)). The INTERMACS score was developed by the INTERMACS Coordinator's Council in order to improve the clinical characterization of device recipients. Seven profiles have been defined for the INTERMACS registry ranging from *crash-and-burn* patients (INTERMACS 1) to patients with advanced NYHA III (INTERMACS 7).

Measures

Health status

The Kansas City Cardiomyopathy Questionnaire (KCCQ) was used to assess disease-specific subjective health status. The KCCQ is a 23-item, self-report questionnaire that quantifies physical limitation, symptoms, and social and role functioning of patients with heart failure. Scores are transformed into a score from 0 to 100, with a higher score representing better health status. The validity and reliability of the KCCQ have previously been established and the measure is highly sensitive to clinical change in heart failure patients over a 6-12 week period.[20-22] In the KCCQ, a Clinical and Overall Summary score can be calculated. The Clinical Summary score is derived from the symptom and physical limitation domain. The Overall Summary score is derived from the physical function, symptom (frequency and severity), social function and quality of life domains. For each domain, the validity, reproducibility, responsiveness and interpretability have been independently established. The absolute difference between baseline and 6-month KCCQ overall summary scores was calculated and dichotomized, with an improvement of ≥10 points indicating a moderately large clinically significant difference in health status.[22] Poor health status was defined as a KCCQ score <50 points.

Health status was also measured using the 12-item Short Form Health Survey (SF-12), with these 12 questions overlapping with the SF-36.[23] These include questions concerning physical functioning, role limitations because of physical health problems or emotional problems, general mental health, bodily pain, general health perceptions, vitality and social functioning. Scoring algorithms are applied to produce the Physical Component Summary (PCS) and Mental Component Summary (MCS) scores. The scoring range is from 0-100 with 100 being the best possible health status. Test-retest (2-week) correlations of 0.89 and 0.76 were observed for the PCS and the MSC, respectively, in the general US population (n= 232). Reliability statistics of the MCS and PCS scales are good with Cronbach's alpha= 0.84 and 0.87, respectively.[24]

Depression and anxiety

The Patient Health Questionnaire (PHQ-9) was used to measure depressive symptoms. This is a 9-item questionnaire with items mirroring the diagnostic criteria for major depressive disorder. Patients are asked to rate how often each symptom has bothered them during the past 2 weeks on a scale from 0 *(not at all)* to 3 *(nearly every day)* (score range 0-27).[25] Patients who score ≥10 are considered to have moderate to severe depressive symptomatology. The PHQ-9 is an ideal instrument for measuring depressive symptoms because it is brief, responsive to change over time, and has good reliability (Cronbach's alpha = 0.86) and validity in medical outpatients and patients with HF.[25,26] The Generalized Anxiety Disorder 7-item scale (GAD-7) is a seven-item self-report measure with items rated on a scale from 0 (not at all) to 3 (nearly every day) (score range from 0-21).[27] A score ≥10 has a sensitivity of 68% and specificity of 88% for detecting generalized anxiety, posttraumatic stress, panic, and social anxiety disorders. The GAD-7 has good psychometric properties (Cronbach's alpha= 0.79-0.91) and has been used successfully in patients with cardiovascular disorders.[27, 28] The PHQ-9 and GAD-7 were measured at baseline, 3, 6 and 12 months follow-up.

Statistical analyses

We used a multilevel model procedure (covariance model: *unstructured*, maximum likelihood (ML) estimate) in SPSS version 19.0 to examine differences in KCCQ Clinical Summary score (KCCQ-CS), KCCQ Overall Summary score (KCCQ-OS), physical health status

(PCS) and mental health status (MCS) from baseline to 3, 6 and 12 months. Due to the chosen statistical analysis, data from all available time points are used, thereby limiting bias and preserving statistical power. Predictors of KCCQ-CS, KCCQ-OS, PCS and MCS were entered in five consecutive models. The first model is the *unconditional means model* in which only the health status scores were entered. In Model 1 time is added to the model as a fixed and random variable thereby creating the *unconditional growth model.* By allowing random effects for the health status scores, there is no longer only a mean value of all patients in health status scores of time, but also an individual health status trajectory for each LVAD patient. This enables the comparison of scores within an individual patient between time points, but also the comparison of the scores of individual patients over time with the scores of other patients over time. Time was divided into two linear effects, one effect between baseline and 3 months follow-up and another effect between 3 and 12 months follow-up. As the second linear effect of time showed no significant unexplained variance, this effect was not included as a random factor in the model. In Model 2, Model 1 was expanded by adding the socio-demographic variables age, gender and status of employment prior to LVAD implantation. In Model 3, the first model was complemented by markers of disease severity: LVEF, INTERMACS gradation, comorbidity and etiology. In Model 4 the psychological factors depression and anxiety were added to Model 1. Finally, in Model 5 all models were combined creating one full model with socio-demographic, clinical and psychological predictors.

The choice of covariates was based on theoretical evidence of possible predictors in health status of LVAD patients.[29, 30] All socio-demographic and clinical variables were entered into the model as fixed effects to examine whether they were associated with overall health status scores over time but also with individual variation in health status scores. Anxiety and depression were entered as time-varying variables, with different scores on baseline, 3, 6 and 12 months follow-up. The results of the association between health status scores and the predictors are indicated by symbols ranging from $p<.10$ (weak association), to $p<.05$ (significant association) and $p<.01$ (strongly significant association).

RESULTS

Patient characteristics

Of the 107 patients who met the inclusion criteria from all three centers, 31 patients refused participation, 18 patients died or were too ill at the time of inclusion, 3 were excluded due to inability to write and read Dutch or English, 1 was excluded due to low intellectual functioning, and 1 patient underwent a heart transplantation shortly after LVAD implantation, leaving a sample of 54 patients for analyses. The patients not participating in the study did not differ on age, gender and type of LVAD compared to patients who participated ($p>.05$). The mean age of the study sample was 54.2±9.4 years and 40 (74%) patients were male. The underlying heart failure etiology was ischemic in 25 (46%) patients and the mean LVEF was 18.0±6.9. The majority of patients received a HeartMate II (n=34, 63%) and the other patients a HeartWare device (n=20, 37%). Medication included ACE-inhibitors/angiotensin receptor blocker (70%), beta-blockers (59%), loopdiuretics (72%) and statins (52%). Complete information on the demographic and clinical characteristics of the patients is shown in **Table 1**.

Table 1: Clinical characteristics of LVAD patients at baseline

	LVAD patients (n=54)
	Mean±SD; N (%)
Socio-demographics	
Male	40 (74)
Age (yrs)*	54.2±9.4
Having a partner	49 (90)
Secondary school and above	49 (90)
Employed	20 (38)
Clinical	
Type of LVAD	
HeartMate II	34 (63)
HeartWare	20 (37)
Length of hospitalization stay (in days)*	49±43
INTERMACS gradation	
1	7 (13)
2	19 (35)
3	19 (35)
4	6 (11)

Etiology	25 (46)
Dilated	20 (37)
Other (hypertrophic, myocarditis)	9 (17)
Previous CABG	7(13)
Previous PCI	18 (33)
Previous valve replacement	6 (11)
Previous myocardial infarction	25 (46)
Previous ICD/CRT-D implantation	39 (72)
Previous CVA	7 (13)
GFR*	54.7±34.5
LVEF*	18.0±6.9
IABP	7 (13)
ECMO	6 (9)
Comorbidity Index	
0	4 (7)
1	6 (11)
2	7 (13)
3	14 (26)
4	10 (19)
≥5	13 (24)
BMI*	24.3±4.1
Medication use	
Amiodarone	38 (70)
Beta blockers	32 (59)
Angiotensin-converting enzyme inhibitors	38 (70)
Statins	28 (52)
Coumarin (derivates)	54 (100)
Lisdiuretics	39 (72)
Psychological	
Depression (PHQ-9)*	4.4±4.8
Anxiety (GAD-7)*	6.9±4.5

**Represented as means ± SD*

CABG= coronary artery bypass graft; PCI= percutaneous coronary intervention; ICD= implantable cardioverter defibrillator; CRT-D= cardiac resynchronization therapy; CVA= cerebrovascular accident; NYHA= New York Heart Assocation; LVEF= left ventricular ejection fraction; IABP= intra-aortic balloon pump; ECMO=extracorporeal membrane oxygenation

Change in health status during the 12-month follow-up period

The mean KCCQ-CS and KCCQ-OS scores are shown in **Figure 1a**. The mean scores on the KCCQ Overall Summary Score were 48±19 at baseline, 70±20 at 3 months, 72±23 at 6 months and 64±20 at 12 months. For the KCCQ Clinical Summary Score this was 47±19, 68±18, 70±21 and 65±20, respectively. The mean scores on the KCCQ-OS and KCCQ-CS improved over 20 points, or 48.5% and 46.8%, respectively. Of the 54 patients, 30 (55.6%) had poor health status (KCCQ score <50 points) at baseline. The scores on both subscales showed an increase from baseline to 3 and 6 months follow-up leading to KCCQ scores which are in concordance with patients having NYHA class II.[21] However, the scores tended to decrease again between 6 months and 12 months follow-up. Based on an improvement of ≥10 points on the KCCQ-OS between baseline and 6 months follow-up, 39 patients showed a moderate to large clinically significant improvement (72%) while 15 patients did not (28%). Patients with and without a clinically significant improvement did not differ on demographic and clinical variables, except for responders having a higher educational level than non-responders (responders 25% vs. 3% in non-responders, χ^2=5.44, p=.02 respectively).

Changes in the mean PCS and MCS scores during the 12-month follow-up are shown in **Figure 1b**. The mean baseline PCS score was 30.5±1.2 and the MCS score was 39.3±1.5. The scores on the PCS and MCS increased between baseline and 3 months, indicating an improvement in physical and mental health status, but stabilized after 3 months follow-up.

Independent predictors of mean health status scores over time

The mean scores on the KCCQ and SF-12 showed a significant effect of time between baseline and 3 months follow-up caused by a strong increase in the KCCQ Clinical and Overall Summary score (KCCQ-CS F=33.49, p<.001; KCCQ-OS F=31.13, p<.001), physical health status (PCS F=31.59, p<.001) and mental health status (MCS F=21.77, p<.001). There was no significant differences in mean scores over time between 3 months and 12 months follow-up (p>.05 for all) **(Table 2)**. After adding the socio-demographic predictors, being employed prior to LVAD implantation was associated with higher scores on the KCCQ-OS (F=9.58, p=.003), KCCQ-CS (F=7.15, p=.01) and PCS (F=7.24, p=.01).

Figure 1a: Mean KCCQ scores over time

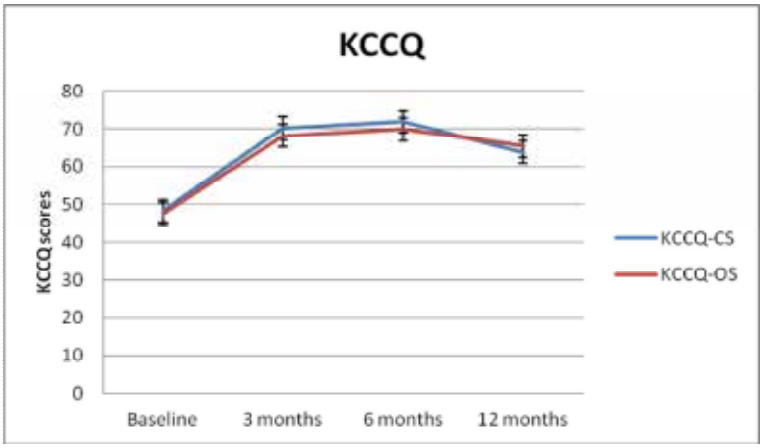
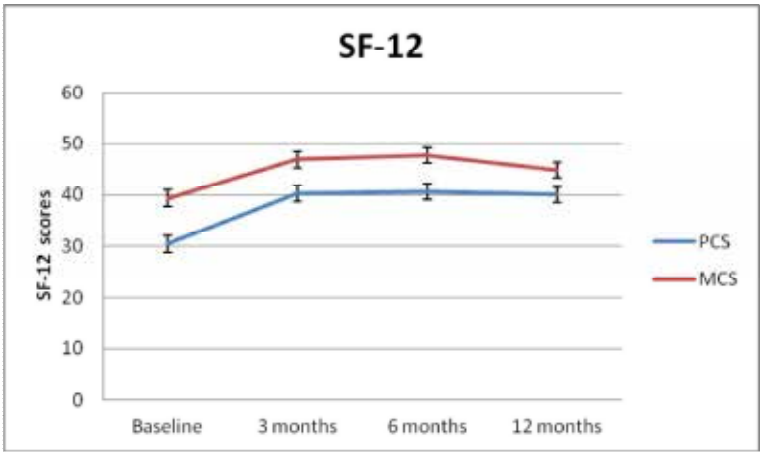


Figure 1b: Mean SF-12 scores over time



Male gender was associated with higher scores on the MCS, however this association was only marginally significant (MCS F=4.04, p=.05). Age did not predict changes in health status over time. From the clinical predictors in Model 3 a non-ischemic etiology was associated with higher scores of KCCQ-OS (F=8.04, p=.008), PCS (F=6.51, p=.015) and MCS (F=8.20, p=.007) over time. A higher number of co-morbidities was associated with a lower MCS (F=9.56 p=.004).

Table 2: Mixed multivariable modeling - significant covariates KCCQ response over time

		KCCQ-OS	KCCQ-CS	PCS	MCS
Model 1	3 months vs. baseline	+++	+++	+++	+++
	3 months vs. 6 and 12 months	O	O	O	O
Model 2	Older age	O	O	O	O
	Male gender	O	O	O	+
	Employed	+++	++	+++	O
Model 3	Higher EF	O	O	O	O
	INTERMACS	O	O	O	O
	Ischemic etiology	---	O	---	---
	Comorbidity	O	O	O	---
Model 4	Depression	---	---	---	---
	Anxiety	O	O	O	--
Model 4	Older age	O	O	O	--
	Male gender	O	O	O	-
	Employed	O	O	O	O
	Higher EF	++	O	O	O
	INTERMACS	O	O	O	O
	Ischemic etiology	O	O	O	O
	Comorbidity	O	O	O	---
	Depression	---	---	---	---
	Anxiety	O	O	O	--

Model 1: unconditional growth model (time)
Model 2: Model 1 + socio-demographic factors
Model 3: Model 1 + clinical factors
Model 4: Model 1 + psychological factors
Model 5: Model 1 + Model 2 + Model 3 + Model 4
O= no association, p >.10
− = negative association, p <.10; −− = negative association, p <.05; −−− = negative association, p<.01
+ = positive association, p <.10; ++ = positive association, p < .05; +++ = positive association. P < .01

In Model 4 the depression and anxiety scores of the LVAD patients over time were entered into the model. Depression, but not anxiety, was a significant predictor of health status scores over time (Model 4: p<.001 for all). An increase of 1 point on depression was associated with a 1-3 point decrease in health status.

In the final model (Model 5) all predictors were entered simultaneously. Higher scores on depression over time were associated with a lower mean health status (KCCQ-OS F = 50.85, *P* <.001; KCCQ-CS F = 33.15, *P* <.001; PCS F=29.62, p<.001; MCS F=22.06, p<.001). A

higher LVEF was associated with better KCCQ Overall Summary Score (F=4.60. p=.04), while older age, more comorbidity and higher scores on anxiety were associated with a lower mental health status (F=5.34, p=.026; F=12.49, p=.001 and F=5.90, p=.017, respectively.

Independent predictors of between and within-person variance of health status scores over time

The individual health status trajectories of each LVAD patient can be used to examine differences between a patient's own scores over time, which is known as the within-person score variance, and differences between the scores over time of individual patients, which is known as the between-person score variance. The *unconditional means model* (without any predictors) of the health status scores show a significant within (*KCCQ-OS*: Wald z=7.40, p<.001; *KCCQ-CS*: Wald z=7.38, p<.001; PCS: Wald z=7.35, p<.001; MCS: Wald z=7.15, p<.001) and between-person variance (*KCCQ-OS*: Wald z=2.69, p=.007; *KCCQ-CS*=1.88, p=.05; PCS: Wald z=2.85, p=.004; MCS: Wald z=2.74, p=.006), indicating that the individual LVAD patients differ significantly from each other on the trajectory of KCCQ and SF-12 scores over time. Based on the unconditional means model, the estimated proportion of within- versus between person variance was 3:1, indicating that most of the difference in health status scores over time is attributable to differences within a patient over time.

In order to explain the within and between-person variance in health status scores, socio-demographic, clinical and psychological predictors were added. Similar to linear regression, R^2 statistics can be computed to quantify how much of the outcome variations are explained by the predictors added to the model. After adding these predictors the within-person variance is reduced by 53.4% for the KCCQ-OS, 35.8% for the KCCQ-CS, 38.6% for the PCS and 38.9% for the MCS. The majority of this variance is explained by the scores of depression and anxiety over time (>50%). The between-person variance is reduced by 41.9%, 36.2%, 23.2% and 82.6% for the KCCQ-OS, KCCQ-CS, PCS and MCS, respectively. The between-person variance for the MCS scores is no longer significant (p=.21), indicating that Model 5 explains the majority of variance in MCS scores found between the LVAD patients.

Overall, the individual trajectories indicate that patients with a stronger incline in KCCQ scores between baseline and 3 months follow-up also continue to have higher scores after 3 months compared to patients with a less strong incline in KCCQ scores between baseline and 3 months.

DISCUSSION

The findings of this study indicate that the majority of LVAD patients experience a moderate to large improvement in health status between LVAD implantation and 12 months follow-up, which is not only statistically significant but also clinically relevant. The mean scores on the KCCQ-OS and KCCQ-CS over time showed a significant increase between LVAD implantation and 3 months follow-up, while the scores tended to stabilize or slightly decrease between 3 months and 12 months follow-up. This effect was also seen in the scores on physical and mental health status, as assessed with the SF-12. The multilevel analyses showed that higher scores on depression over time were associated with a lower mean health status on the KCCQ-OS, KCCQ-CS, PCS and MCS. A higher LVEF was associated with better KCCQ-OS, while older age, more comorbidity and higher scores on anxiety were associated with poorer mental health status, respectively. Furthermore, there were significant differences in the health status scores over time within and between LVAD patients. The within-person variance in health status scores was mostly explained by variance in scores on depression and anxiety, and not by clinical factors. The majority of the between-person variance of the MCS, but not the KCCQ-OS, KCCQ-CS and PCS, was explained by the socio-demographic, clinical and psychological factors included in the model.

Despite an increasingly growing number of patients being implanted with an LVAD around the world, there is minimal information on patient-reported outcomes such as health status, especially concerning the within- and between person changes in health status scores and the predictors of health status. Our results indicate that scores on health status of Dutch and Canadian LVAD patients, as measured by the KCCQ, are consistent with those found in the HeartMate II trial[11, 14, 17, 31, 32] and by Aaronson et al.,[10] except for slightly higher KCCQ-OS scores at 3 and 6 months follow-up. For this comparison, it was taken into account that the baseline measurement for health status in these trials was performed before LVAD implantation, therefore our baseline measurement was compared to the 1 month follow-up in these studies. No differences were found on the KCCQ scores for gender and age, which is consistent with the findings of others.[11, 16] As the INTERMACS registry used the EQ-5D to measure health status the outcomes of this study cannot directly be compared to theirs. However, the EQ-5D does show a similar health status trajectory compared to the KCCQ with a steep incline between baseline and 3 months which is maintained during the first year after implantation.[12, 15] The generic health status measure (i.e., the SF-12) allows for the

comparison between various patient populations. Only the study of Kugler et al. used the extended version of the SF-12 (i.e. SF-36) to examine the impact of a multi-model intervention for LVAD patients. Scores on the PCS and MCS were identical with our findings with PCS scores ranging from 30 to 40 points and MCS scores ranging from 45 to 50 points.[2] The LVAD patients scored considerably lower compared to the Dutch normative population (MCS: 51±9, PCS: 51±9; age 50-59), but did score the same as post-MI patients without LVAD implantation.[33]

The main goal of this study was to examine potential predictors of the mean and individual health status scores over time. Except for Grady et al.,[30] no other studies on LVAD patients have examined the predictors in health status scores. Grady et al. also found that psychological stress was a strong predictor of health status after LVAD implantation. As is known from previous studies[30,34,35] psychological distress is highly prevalent in LVAD patients post-implantation. This may be attributed to the challenges that patients face particularly shortly after implantation, including complications, cardiac rehabilitation and medication, driveline- and device-training, which could make them more vulnerable to distress. Based on the results of this study, it seems that not only psychological distress shortly after implantation is an important predictor for health status scores but also the change in psychological distress scores over time. As a subset of LVAD patients (≈25%) seems to suffer from chronic psychological stress following discharge from the hospital,[36, 37] this subset of patients is likely to be more vulnerable for lower health status outcomes. Hence, due to the strong interplay between psychological distress and health status, it seems important to monitor psychological distress in patients in order to prevent adverse outcomes.

Also, comorbidity and LVEF were found to be important predictors for poor health status. In a study population with a relatively high prevalence of comorbidities (e.g. lipid dysfunction, diabetes and hypertension), it can be expected that comorbidities add significantly to the burden after LVAD implantation, and could therefore be important antecedents for lower health status scores. Interestingly, the INTERMACS score of patients did not affect the trajectory of health status scores after LVAD implantation, suggesting that the increase in health status for patients with INTERMACS category 1 and 2 is at least as strong as those of patients with INTERMACS category >3. Similar findings were also reported recently by Grady et al.[38]

The variance in health scores over time within and between the LVAD patients was significant and could only be partly explained by the predictors in the model, suggesting that more factors should be explored. Other potential predictors who might explain the variance in health status could be other LVAD-related factors, such as adverse medication effects or clinical complications (i.e., ventricular tachyarrhythmia, infection) requiring hospitalization. However, there are also factors that can affect health status that are not LVAD-related such as psycho-social factors (i.e. coping, personality, marital quality, self-efficacy, locus of control, social isolation). Identifying these factors is important in order to delineate a profile of high-risk patients who may benefit less from LVAD implantation. These patients could then be offered more intensive support or care and may benefit from adjunctive interventions.

Limitations of this study include the relatively small sample size and the relatively few number of female LVAD patients. Due to the sample size, it was not possible to include numerous predictors of health status scores (i.e., complications, social-support) nor perform a latent class analysis categorizing patients into reduced, stable or improved health status over time. Furthermore, due to the sample size it was also not possible to stratify our results for type of LVAD or site of implantation. As the clinical and psychological care of LVAD patients might differ slightly between the centers this could have impinged on our results. As shown in other studies, patients who refused to participate in our study might have suffered from more impaired health status and psychological distress, with the possibility that the results could represent an overestimation of the health status experienced by patients.[39] Finally, we used self-report measures of psychological distress rather than a clinical diagnostic interview.

CONCLUSION

The primary target of LVAD therapy is to improve survival and well-being of patients with end-stage heart failure. As indicated by the findings of the current study, we found a significant improvement in health status after LVAD implantation. However, there were large differences in individual health status score trajectories which are only partially explained by measures of disease severity pre-LVAD, comorbidity and psychological distress. Hence, although LVADs may solve the problem of donor scarcity, it is important not to lose sight of the impact of treatment on patients and thus continue to seek ways that may help to keep

improving their well-being and quality of life. In order to better predict the post-implantation course, enhance the quality of care and improve the outcomes after LVAD therapy, future research is warranted that examines a broader range of clinical and psycho-social predictors of changes in health status scores over time and whether these changes are associated with long-term outcomes in LVAD therapy.[18]

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CHAPTER 5

Health status and psychological distress in patients with noncompaction cardiomyopathy: The role of burden related to symptoms and genetic vulnerability

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ABSTRACT

Background: Because of its genetic underpinnings and physical disease burden, non-compaction cardiomyopathy (NCCM) is expected to be associated with a lower health status and increase in psychological distress. Here, we determined the health status and psychological distress in NCCM patients, and disentangled the role of genetic predisposition versus NCCM-related symptom burden by comparing NCCM patients with (1) patients with familial hypercholesterolemia (FH), and (2) patients with acquired dilated cardiomyopathy (DCM)

Methods: NCCM patients (n=45, mean age 46.7±15.1, 38% male) were compared with 42 DCM and 43 familial hypercholesterolemia patients using a case-control design matching for age and sex. Outcome measures were health status (Short Form Health Survey-12), anxiety (Generalized Anxiety Disorder 7-item scale) and depression (Patient Health Questionnaire 9-item scale).

Results: NCCM patients showed significantly worse health status (PCS $F(1,84))=9.58$, $p=.003$; MCS $F(1,84)=16.65$, $p<.001$), anxiety ($F(1,85)=9.63$, $p=.003$) and depression scores ($F(1,82)=5.4$, $p=.023$) compared to familial hypercholesterolemia patients, also after adjusting age, sex, comorbidity, educational level and time since diagnosis. However, NCCM patients did not differ from DCM patients ((PCS $F(1,82)=2,61$, $p=.11$; MCS $F(1,82)=.55$, $p=.46$), anxiety ($F(1,82)=1.16$, $p=.28$) and depression ($F(1,82)=1,95$, $p=.17$)).

Conclusion: The cardiac symptoms of NCCM are mainly responsible for the observed poor health status and elevated anxiety and depression associated, instead of the genetic nature of a NCCM diagnosis.

INTRODUCTION

Noncompaction cardiomyopathy (NCCM) is a relatively new and rare disease entity characterized by prominent trabecular meshwork and deep intertrabecular recesses of the left ventricular walls.[1-4] NCCM is classified as a primary cardiomyopathy and is a potentially life-threatening condition because of its association with progressive left ventricular dysfunction, heart failure, ventricular and supra-ventricular arrhythmias, embolic events and sudden cardiac death, with a 5-year mortality rate up to 50%.[5-7] The clinical presentation of NCCM is variable from asymptomatic to severe LV decompensation or life-threatening arrhytmias.[6] Key characteristics of NCCM are the relatively young age of the patients, the poor clinical prognosis in symptomatic individuals, the need for detailed imaging, DNA diagnostics, familial screening, and genetic counseling.[4] Most cases of NCCM are familial with an autosomal dominant inheritance pattern.[8-12] NCCM can therefore be detected in asymptomatic individuals based on familial screening or following diagnostic tests related to other (non-)cardiovascular conditions. The treatment of NCCM involves pharmacological treatment, including heart failure medication, symptom management and prevention of adverse long-term events by implantable cardioverter defibrillator placement and anticoagulation therapy.[3, 6]

Little is known about the psychological and behavioral effects of living with a diagnosis of NCCM. Both perceived distress related to adverse disease progression as well as genetic burden of cardiovascular diseases may adversely influence quality of life and general wellbeing. In patients with genetic risk for other disorders a wide range of psychological reactions have been described, including anxiety, worry about risk to children, guilt, anger, uncertainty, sadness, and depression.[13,14] Because of its genetic underpinnings, it is likely that NCCM is associated with emotional and psychosocial challenges in addition to potential physical disease burden, which to date has not been investigated. This study examines to which extent psychological factors are adversely influenced by NCCM. We will differentiate between issues related with the genetic nature of the disorder and those related to the NCCM-related symptom burden. To disentangle the potential psychological impact associated with the genetic nature of NCCM relative to the heart failure symptoms, the NCCM patients were compared with (1) patients with autosomal dominant familial hypercholesterolemia, and (2) acquired dilated cardiomyopathy patients with a history of heart failure, who were matched as group for sex and age in this case-control study.

METHODS

Study population and design

Consecutive outpatients with a diagnosis of NCCM were recruited from the Erasmus Medical Center, Rotterdam, the Netherlands between May 2012 and August 2013. Inclusion criteria were a diagnosis of NCCM based on stringent echocardiographic data (and extended by magnetic resonance imaging as needed) as described by the criteria of Jenni et al.[1], aged ≥18 years. Exclusion criteria were >80 years of age, unable to understand and read Dutch, other life-threatening diseases, and cognitive impairments or psychiatric comorbidity (except for mood disorders).

The first comparison group included patients with familial hypercholesterolemia (FH). Because of the genetic nature of the disorder associated with increased levels of low-density lipoproteins, these patients are prone to develop cardiovascular diseases. Patients in this comparison group were not included if they had documented coronary artery disease or a left ventricular ejection fraction (LVEF) <40%.

The second comparison group included patients with dilated cardiomyopathy (DCM) and a history of heart failure. This comparison group was used to determine the contribution of a positive history of cardiac disease and symptom burden as related to the NCCM group. These patients were identified via the Erasmus Medical Center institutional heart failure database with diagnosis verified by echocardiography and clinical history. Patients with coronary artery disease as primary cause were excluded from this control group. Both control groups were matched on sex and age using frequency matching.

Of the 105 NCCM patients registered in the Erasmus MC database 56 could be contacted for study participation, 11 patients refused participation or did not return the baseline questionnaire, leaving 45 patients eligible for analyses (79% response rate). For the familial hypercholesterolemia group 55 patients were approached, 12 patients refused participation or did not return the questionnaire leaving 43 patients for analysis in this group. For the cardiomyopathy group 54 patients were approached, 12 patients refused participation or did not return the questionnaire, resulting in a sample of 42 patients in this group.

The study protocol was approved by the medical ethics committee of the Erasmus Medical Center, the Netherlands. The study was conducted according to the Helsinki Declaration and all patients provided written informed consent. All patients were

approached, for study participation, by their treating physician or heart failure nurse. Patients received a package containing written information about the study, an informed consent form, and the questionnaire booklet together with a postage-paid return envelope at their home address. If the questionnaire package was not returned within two weeks, participants received a reminder telephone call.

Measures

Health status and quality of life

Health status was measured using the 12-item Short Form Health Survey (SF-12), which these 12 questions overlapping with the SF-36.[15] These include questions concerning physical functioning, role limitations because of physical health problems or emotional problems, general mental health, bodily pain, general health perceptions, vitality and social functioning. Scoring algorithms are applied to produce the Physical Component Summary (PCS) and Mental Component Summary (MCS) scores. The scoring range is from 0-100 with 100 being the best possible health status. Test-retest (2-week) correlations of 0.89 and 0.76 were observed for the PCS and the MSC, respectively, in the general US population (n=232).[16] Reliability statistics of the MCS and PCS scales is good with Cronbach's alpha= 0.84 and 0.87, respectively.

Depression

The Patient Health Questionnaire (PHQ-9), was used to measure depressive symptoms. This is a 9-item questionnaire with the items mirroring the diagnostic criteria for major depressive disorder. Patients are asked to rate how often each symptom has bothered them during the past 2 weeks on a scale from 0 *(not at all)* to 3 *(nearly every day)* (score range 0-27). Patients who score a 10 or higher are considered to have moderate or greater depressive symptoms.[17] The PHQ-9 is an ideal instrument for measuring depressive symptoms because it is brief, responsive to change over time, and has good reliability (Cronbach's alpha = 0.86) and validity in medical outpatients and patients with HF.[18]

Anxiety

The Generalized Anxiety Disorder 7-item scale (GAD-7) is a self-reported seven-item anxiety scale rated on a scale from 0 *(not at all)* to 3 *(nearly every day)* (score range from 0-21). A

score of 10 or higher has a sensitivity of 68% and specificity of 88% for detecting generalized anxiety, posttraumatic stress, panic, and social anxiety disorders.[19] The GAD-7 has good psychometric properties (Cronbach's alpha = 0.79-0.91) and has been used successfully in patients with cardiovascular disorders.[20]

Clinical and demographic variables

Information on these demographic and clinical variables was extracted from purpose-designed questions in the questionnaires and from patients' medical records. Information on demographic variables comprised gender, age, marital status (having a partner vs. having no partner), and educational level (primary school vs. secondary school and above). Information on clinical variables included time since diagnosis, previous cardiac events, prescribed medications (beta-blockers, calcium antagonists, nitrates, aspirin and other platelet-aggregation inhibitors, anticoagulants, ACE-inhibitors, statins, loopdiuretics and psychotropic medication), standard laboratory values (creatinine, C-reactive protein, nt-proBNP, white blood cell count), alcohol and cigarette use, and BMI. The comorbidity index was calculated in accordance with the original Charlson Comorbidity Index (CCI) in which a weight of 2 was assigned to renal failure and any malignancy, and a weight of 1 to the other comorbid conditions (i.e. diabetes mellitus, cerebrovascular accident, peripheral arterial disease), depending on the relative mortality risk of each specific disease. By adding up the values assigned to each comorbid condition, a comorbidity score was calculated for each patient. Because age is a risk factor for mortality independent of the presence of comorbid conditions, we adjusted the score by adding one point to the score for each decade of life over the age of 50 at time of study entry.[21] Kidney failure was measured by calculating the glomerular filtration rate of creatinine (GFR_{creat}) using the MDRD formula, and kidney dysfunction was defined as a GFR_{creat}<60mL/min per 1.73m^2.[22] For the NCCM and CMP patients also data on New York Heart Association (NYHA) functional class was collected.

Statistical analyses

Data are presented as mean ± standard deviation (SD) or N and %. To compare the demographic and clinical characteristics between the NCCM, FH and DCM patients, *t* tests, Mann-Whitney U tests, or χ^2-tests were used depending on the measure and variable distribution. Continuous scores for health status, anxiety and depression of the three groups

were compared using multivariate analyses of variance (MANOVA). If the overall MANOVA effects were significant subsequent analyses of covariance (ANCOVAs) were used to compare NCCM vs. FH and NCCM vs. DCM, adjusting for covariates that are known to be associated with health status and psychological factors in patients with cardiovascular disease. In adjusted analyses time since diagnosis, marital status, educational level and comorbidity, as measured using the Charlson Comorbidty Index, were entered as covariates. These analyses were repeated comparing only the NCCM and DCM group, thereby also adding NYHA classification and dosage of loopdiuretics as additional covariates. In addition the NCCM and DCM group was stratified based on disease severity using unadjusted analyses of variance (ANOVA). Furthermore, the scores for depression and anxiety were dichotomized based on the validated cut-off score of ≥10[17, 19] and compared using χ^2-tests. Data were analyzed using SPSS Version 19.0. A p-value of < 0.05 was considered statistically significant.

RESULTS

Patient characteristics

Table 1 shows that the three groups were comparable in terms of socio-demographic variables (p>.05) and that the matching procedures for sex and age were successful. The NCCM and DCM patients had significantly elevated measures on most biomedical measures as compared to the FH group with a higher prevalence of ICD/CRT-D implantations, comorbidities and use of loopdiuretics, beta-blockers and ACE-inhibitors (p<.001 for all). Furthermore, NCCM and DCM patients had a shorter time since diagnosis (p=.01) and a lower prevalence of alcohol consumption (p=.02) and statin use (p<.001). Comparisons between NCCM and CMP groups revealed that NCCM patients are prescribed significantly less loopdiuretics (p=.005) and ACE-inhibitors (p=.04). Compared to the familial hypercholesterolemia group, NCCM patients are more often implanted with an ICD/CRT-D (p<.001), have more co-morbidities (p=.002), are prescribed more ACE-inhibitors (p<.001), β-blockers (p<.001) and loopdiuretics (p<.001), and use less statins (p<.001) and alcohol (p=.007).

Table 1: Socio-demographic and clinical characteristics of NCCM, dilated cardiomyopathy and familial hypercholesterolemia patients

	NCCM N=45	DCM N=42	Familial hypercholesterolemia N=43	NCCM vs. DCM and FH p-value	NCCM vs. DCM p-value	NCCM vs. FH p-value
Demographics						
Age (years)	46.7±15.1	48.8±15.5	47.8±15.8	.83	.45	.64
Gender (males)	17 (38)	17 (40)	17 (39)	.99	.91	.80
Having a partner	32 (71)	33 (79)	32 (74)	.43	.20	.78
Higher education[†]	41 (91)	35 (83)	40 (94)	.50	.62	.45
Currently employed	19 (42)	17 (40)	27 (61)	.13	.94	.07
Clinical factors						
Body Mass Index	24.9±3.5	25.8±5.4	26.4±4.7	.35	.37	.07
NYHA class II/III	20 (45)	23 (55)	-	-	.51	-
LVEDD (mm)	59±8	56±9	-	-	.08	-
LVESD (mm)	45±10	44±12	-	-	.42	-
LV fractional shortening	23.7±8.9	23.4±8.1	-	-	.86	-
ICD/ CRT-D	33 (73)	27 (66)	0 (0)	**<.001**	.89	**<.001**
GFR (ml/minute/1.73m^2)	77.8±18.1	73.1±20.2	80.7±12.4	.20	.27	.46
COPD	1 (2.3)	4 (10)	4 (10)	.28	.14	.14
Diabetes	1 (2.3)	6 (15)	2 (5)	.07	.04	.52

Smoking	6 (13)	7 (17)	4 (10)	.49	.60	.28
Alcohol	19 (42)	17 (42)	30 (75)	**.02**	.99	**.007**
Time since diagnosis (months)	71±76	86±66	124±102	**.01**	.32	**.01**
Comorbidity Index				**<.001**	.66	**.002**
0	5 (11)	0 (0)	24 (56)			
1	20 (44)	20 (47)	5 (13)			
2	6 (13)	7 (17)	4 (10)			
≥3	14 (33)	15 (36)	8 (21)			
Medication						
Loopdiuretics	17 (30)	28 (68)	0 (0)	**<.001**	**.005**	**<.001**
Beta-blockers	36 (80)	35 (85)	4 (10)	**<.001**	.51	**<.001**
ACE/ARB	22 (49)	29 (71)	5 (12)	**<.001**	**.04**	**<.001**
Oral anticoalugants	28 (62)	25 (64)	3 (7)	**<.001**	.86	**<.001**
Statins	7 (16)	12 (29)	42 (100)	**<.001**	.13	**<.001**
Amiodarone	7 (16)	6 (15)	1 (2)	.22	.57	.14

NCCM= non-compaction cardiomyopathy; DCM= dilated cardiomyopathy; FH=familial hypercholesterolemia; ICD= implantable cardioverter defibrillator; CRT-D= cardiac resynchronization therapy-defibrillator; GFR= glomular filtration rate; COPD= chronic obstructive pulmonary disease; ACE=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker

Health status, anxiety and depression in NCCM

As is shown in **Figure 1**, unadjusted multivariate analysis showed that the three groups differed significantly in terms of health status, anxiety and depression scores (Wilks' Lambda=0.75, F(8,230)=4.40, p<.001). Scores on physical health status (F(8,230)=11.18, p<.001), mental health status (F(8,230)=12.50, p<.001), anxiety (F(8,230)=5.51, p=.005) and depression (F(8,230)=6.4, p=.002) differed between NCCM, DCM and FH patients. When adjusting for age, sex, comorbidity, educational level and time since diagnosis the overall multivariate group effect for all outcome variables combined remained significant (Wilks' Lambda=.80, F(8,220)=3.29, p=.001) **(Table 2)**. Subsequent analyses focus on the comparison between NCCM vs. FH and NCCM vs. DCM patients.

Comparison between patients with NCCM and familial hypercholesterolemia

NCCM patients showed significantly worse health status scores (PCS F(1,84))=9.58, p=.003; MCS F(1,84)=16.65, p<.001) and higher scores on anxiety (F(1,85)=9.63, p=.003) and depression (F(1,82)=5.4, p=.023) compared to FH **(Figure 1)**. Adjustment for age, sex, comorbidity, educational level and time since diagnosis resulted in significant differences between NCCM and FH for mental and physical health status (PCS F(6,78)=6.04, p=.021 MCS F(6,78)=12.69, p=.001) and anxiety (F(6,80)=5.28, p=.02), whereas results for depression became non-significant in adjusted models (F(6,76)=1.67,p=.20). Patients with a shorter time since diagnosis, a higher degree of comorbidity and a lower educational level had significantly lower physical health status scores (p's≤.01). For anxiety and depression a younger age and also a higher degree of comorbidity and a lower educational level were significantly associated with higher scores (p's≤.03) **(Supplementary Table 1a)**. The prevalence of anxiety was significantly higher in NCCM vs. FH (16% vs. 2%; p=03). For depression these percentages were 16% and 2%, respectively (p=.89).

Comparison between NCCM and DCM

NCCM and DCM patients showed no significant difference in health status (PCS F(1,82)=2,61, p=.11; MCS F(1,82)=.55, p=.46), anxiety (F(1,82)=0.36, p=.54) or depression (F(1,82)=1,95, p=.17). Adjustment for age, sex, comorbidity, time since diagnosis and educational level did not alter these findings **(Supplementary Table 1b)**. Additionally, NYHA functional class and the total daily dosage of loopdiuretics were entered into the model to correct for differences

in disease severity. NYHA classification, but not the dosage of loopdiuretics, was significantly associated with lower health status scores (PCS F(1,75)=12.61, p=.001; MCS F(1,75)=6.43, p=.01) and higher depression (F(1,72)=4.86 p=.03) scores. The prevalence of depression was lower in NCCM vs. DCM (18% vs. 32%) but this difference was not significant (p=.13). No differences in anxiety were observed (16% vs. 18%, respectively (p=.73).

The role of symptoms in NCCM, DCM and FH

Because symptom status as measured by NYHA classification was significantly associated with health status, anxiety and depression in the NCCM and DCM group, both groups were stratified by NYHA classification (NYHA I vs. NYHA II/III) thereby creating four groups. Results show a significant group effect (Wilks' Lambda=.67, F(12,188)=2.61, p=.003) and an effect for symptom status on physical health status (F=8.19, p<.001, *Cohen's d*=.21) **(Figure 2)**.

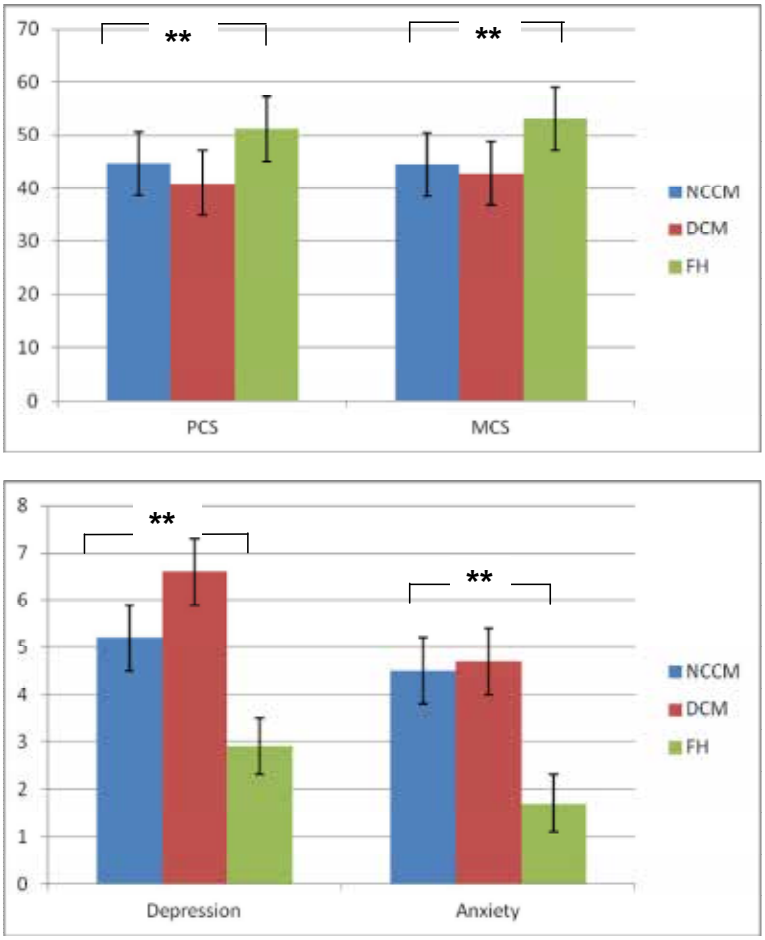
To compare the NCCM with patients with FH (who are asymptomatic), the NCCM patients with NYHA with class I (N=25) were compared to the FH patients. No significant group effect between the NCCM NYHA class I patients and the patients with FH were found (Wilks' Lambda=.86, F(4,58)=2.45, p=.06) except for a lower mental health status (F=7.41, p=.008) and higher levels of anxiety (F=5.33, p=.02) NCCM patients compared to familial hypercholesterolemia patients **(Figure 3)**.

DISCUSSION

NCCM is a relatively new disease entity, contrary to DCM and familial hypercholesterolemia, of which the definition, pathogenesis, treatment and prognosis are still under debate.[23] In the Netherlands the expertise on NCCM is limited with the Erasmus Medical Center being the only center performing research on the clinical as well as the psychological aspects of having a diagnosis of NCCM. As expected, noncompaction cardiomyopathy and dilated cardiomyopathy patients had significantly elevated measures on most biomedical items related to cardiac disease as compared to the familial hypercholesterolemia group. Patients with NCCM also had a significantly lower health status and elevated levels of anxiety and depression compared to patients with familial hypercholesterolemia. However, no significant group effect was found between asymptomatic patients with NCCM and patients with familial hypercholesterolemia, suggesting a critical role of cardiac symptoms in the

observed poor health status and elevated anxiety and depression associated with NCCM. Consistent with this observation is that the NCCM group did not differ from the DCM group on any of the psychological outcome measures and that the main driving factor appeared to be the presence of symptoms (as indicated by NYHA classification) or total daily dose of loopdiuretics. Specifically, stratification of the NCCM and DCM group by NYHA classification showed that patients having NYHA class II/III had lower health status and higher anxiety and depression scores compared to NYHA class I patients, irrespective of having NCCM or DCM.

Figure 1: Means (SE) of health status, anxiety and depression scores NCCM, dilated cardiomyopathy and familial hypercholesterolemia patients (MANOVA)



PCS= physical component scale; MCS= mental component scale; NCCM= non-compaction cardiomyopathy; DCM= dilated cardiomyopathy; FH=familial hypercholesterolemia

Table 2: Adjusted analyses of health status, anxiety and depression in NCCM, dilated cardiomyopathy and familial hypercholesterolemia patients (ANCOVA)

	PCS		MCS		Anxiety		Depression	
	F	**p-value**	**F**	**p-value**	**F**	**p-value**	**F**	**p-value**
NCCM vs. FH vs. DCM	**6.01**	**.003**	**8.59**	**<.001**	.97	.38	3.12	.05
Age	.35	.56	3.28	.07	.32	.58	**5.91**	**.02**
Sex	**4.81**	**.03**	**5.19**	**.03**	.63	.43	3.28	.07
Time since diagnosis (months)	1.87	.17	.32	.57	.004	.95	.03	.87
Educational level	**6.53**	**.01**	2.07	.15	.14	.71	**6.06**	**.02**
Comorbidity	**8.96**	**.003**	1.28	.26	.13	.72	**4.97**	**.03**

PCS= physical component scale; MCS= mental component scale; NCCM= non-compaction cardiomyopathy; DCM= dilated cardiomyopathy; FH=familial hypercholesterolemia

Other studies that have examined the psychological impact of genetic cardiovascular conditions show mixed results, with some studies finding high anxiety and/or depression levels in patients with hypertrophic cardiomyopathy or patients at risk for arrhythmias and sudden cardiac death,[24-26] while other studies found almost no adverse effects on health status or relatively low prevalence's of anxiety and depression compared to the general population.[27-30] Steptoe et al. compared the health status and psychological distress of familial versus non-familial DCM and found that the presence of familial DCM was related to better physical functioning and fewer role limitations related to emotional problems compared to patients without a familial DCM.[31] A reason for this finding could be a difference in disease severity between the familial and non-familial DCM group, as non-familial cases might have experienced more symptoms while familial DCM patients were often asymptotic and diagnosed through genetic family screening. In the current study, there are no such differences in disease severity between the NCCM and DCM patients, thereby possibly explaining the discrepancy in results between the studies.

Overall, the non-significant differences between patients having NCCM and DCM suggest that the presence and severity of symptoms, activity restrictions and possible adverse medication side effects are mainly responsible for the negative effects on health status, anxiety and depression. The health status scores of the familial hypercholesterolemia patients was significantly higher compared to the NCCM and DCM patients, and equal to those of the Dutch normative population.[32] Four other studies on familial hypercholesterolemia patients also found no differences between the health status of familial hypercholesterolemia patients and healthy control populations,[33-37] while one study even found a higher health status scores for familial hypercholesterolemia patients compared to a control population.[38] The prevalence of anxiety in the group of familial hypercholesterolemia was higher compared with the study of Hollman et al. who found a prevalence rate for anxiety of 5%.[38] However, another study found that 44% of the patients expressed anxiety, mainly originating from the fear of developing cardiovascular disease.[39]

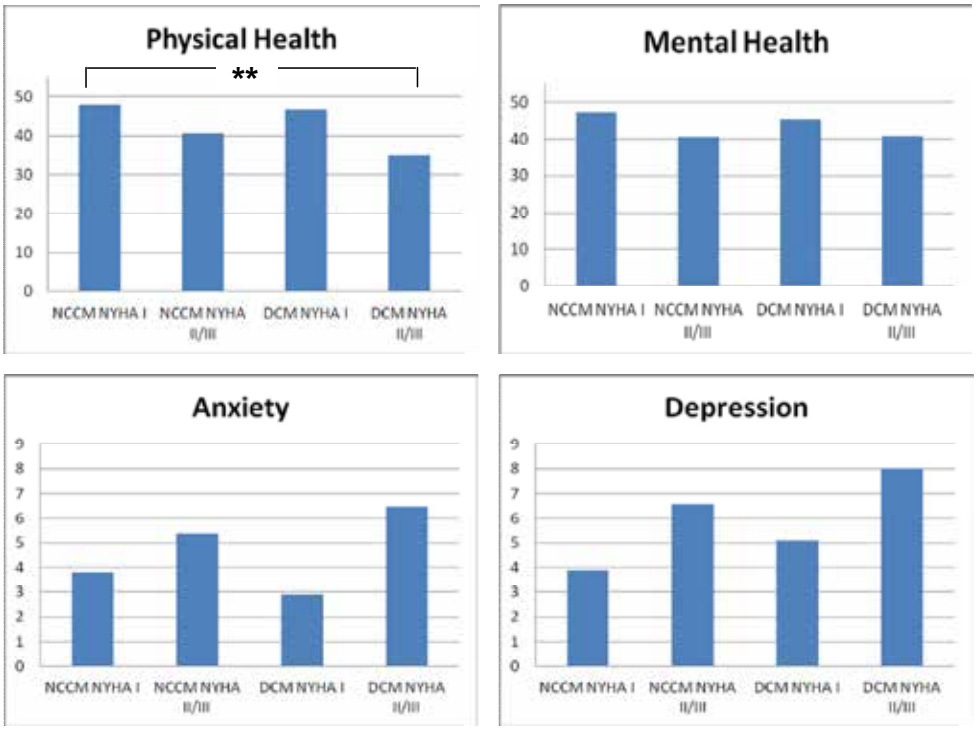
The use of two comparison groups and the well-characterized sample of NCCM patients are strengths of this study. Several limitations need to be considered including the relatively small sample size. Furthermore, this was a single center cross-sectional study which limited the ability to determine the directionality of any relationship between health status, anxiety, depression and the covariates added to the model. Also, for the assessment

of anxiety and depression we used a self-report measure, and caution is required regarding the outcomes of the analyses in relation to a clinical diagnosis of depression. The study did not use performance-based indices of functional status such as treadmill exercise or the six minute walking test.

CONCLUSION

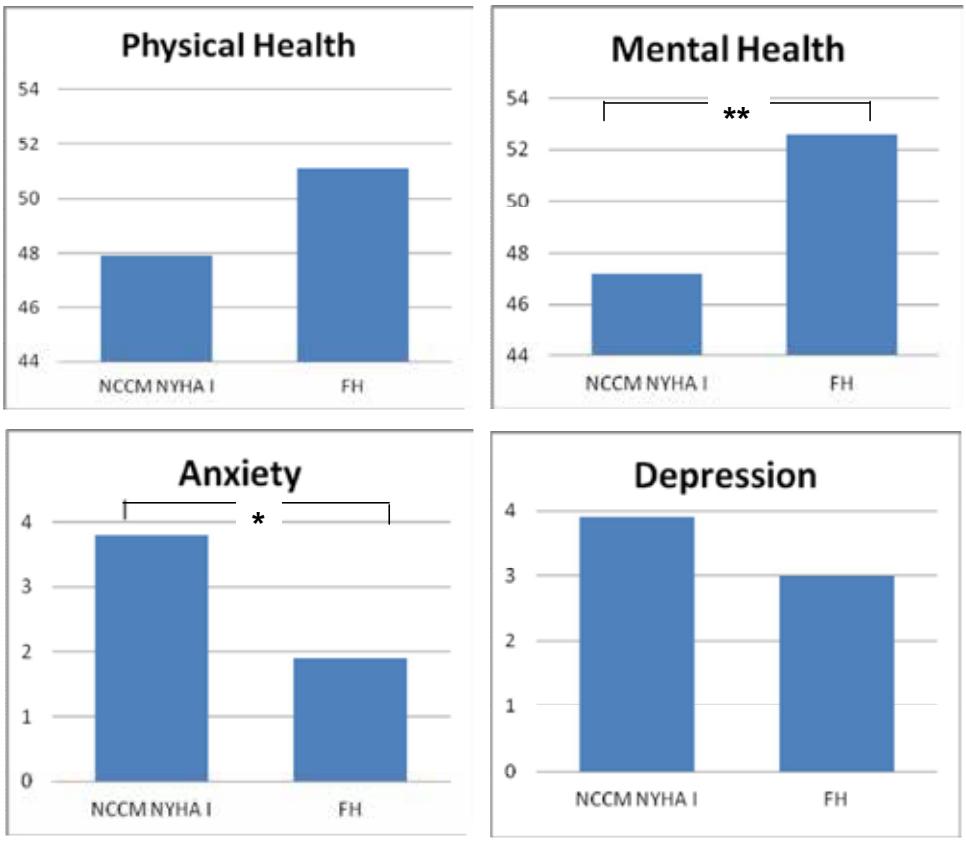
NCCM is a new, potentially life-threatening condition with genetic underpinnings. The prevalence of NCCM will probably increase in the coming years as a result of improved modalities available for cardiac imaging and a higher awareness amongst cardiologists about the nature and presentation of this condition. In the current study we found that NCCM patients have a poorer health status and reported more psychological distress compared to patients having familial hypercholesterolemia while their reported wellbeing was equal to that of DCM patients. These findings indicate that the genetic nature of a NCCM diagnosis does not seem to result in an additional burden with respect to quality of life. Additional studies are warranted to replicate these findings, to examine the role of psychological distress in the course of disease progression and prognosis in NCCM patients, and to explore differences in health status and psychological distress between NCCM and other cardiomyopathies associated with a substantial genetic vulnerability.

Figure 2: Health status, anxiety and depression of <u>NCCM and dilated cardiomyopathy patients</u> stratified by NYHA classification



*PCS= physical component scale; MCS= mental component scale; NCCM= non-compaction cardiomyopathy; DCM= dilated cardiomyopathy; FH=familial hypercholesterolemia; NYHA= New York Heart Association functional class *p<.05, **p<.001*

Figure 3: Health status, anxiety and depression of NCCM and familial hypercholesterolemia patients stratified by NYHA classification



*PCS= physical component scale; MCS= mental component scale; NCCM= non-compaction cardiomyopathy; FH=familial hypercholesterolemia; NYHA= New York Heart Association functional class *p<.05, **p<.001*

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Supplementary table 1a: Comparison of NCCM and familial hypercholesterolemia patients on health status, anxiety and depression (ANCOVA)

	PCS		MCS		Anxiety		Depression	
	F	**p-value**	**F**	**p-value**	**F**	**p-value**	**F**	**p-value**
NCCM vs. FH	**6.04**	**.01**	**12.69**	**.001**	**5.28**	**.02**	1.67	.20
Age	3.13	.08	3.62	.06	**8.32**	**.005**	**9.02**	**.004**
Sex	2.62	.11	.89	.35	.13	.72	.89	.35
Time since diagnosis (months)	**7.15**	**.009**	2.98	.09	2.16	.15	1.63	.21
Educational level	**10.59**	**.002**	3.27	.08	**8.57**	**.004**	**12.52**	**.001**
Co-morbidity	**14.13**	**<.001**	2.33	.13	**5.25**	**.03**	**7.90**	**.006**

Supplementary table 1b: Comparison of NCCM and dilated cardiomyopathy patients on health status, anxiety and depression (ANCOVA)

	PCS		MCS		Anxiety		Depression	
	F	**p-value**	**F**	**p-value**	**F**	**p-value**	**F**	**p-value**
NCCM vs. DCM	1.35	.25	.73	.40	1.10	.30	1.93	.17
Age	.25	.62	1.95	.17	.33	.57	3.71	.06
Sex	**4.28**	**.04**	**5.33**	**.02**	.62	.43	3.03	.09
Time since diagnosis (months)	.06	.81	1.49	.23	.01	.99	.53	.47
Educational level	4.26	**.04**	1.20	.28	.13	.72	**5.84**	**.02**
Co-morbidity	3.38	.07	.15	.70	.14	.71	1.37	.25

PCS= physical component scale; MCS= mental component scale; NCCM= non-compaction cardiomyopathy; DCM=dilated cardiomyopathy; FH=familial hypercholesterolemia

PART TWO

Psychological distress and clinical outcomes of heart failure



CHAPTER 6

Anti-depressant use and risk for mortality in 120,443 heart failure patients with or without a diagnosis of clinical depression

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ABSTRACT

Background: Depression increases the risk for mortality in heart failure (HF) patients. However, effectively treating depression by anti-depressant therapy does not seem to be a guarantee for improving survival. The objectives of the current study were to identify the correlates of anti-depressant use subsequent to hospital discharge, and examine the relation between anti-depressant use, clinical depression and mortality.

Methods and Results: The study sample included 120,443 HF patients from the Danish Patient Registry. In total, 16.6% (19,348) received anti-depressants subsequent to discharge, of which 86.7% (16,780) had no diagnosis of clinical depression and 13.3% (2,568) had a diagnosis of clinical depression. Patients using anti-depressants, with or without clinical depression, had a significantly higher risk for all-cause mortality (HR=1.22; 95%CI, 1.22-1.27; HR=1.25; 95%CI, 1.17-1.27, respectively) as compared to patients not using anti-depressants in adjusted analysis. Female gender, older age, increasing HF severity and number of co-morbidities were also strong predictors for all-cause mortality (p<.001). After adjustment for multiple confounders all anti-depressant groups were independently associated with a higher all-cause mortality risk compared to patients using no anti-depressants (SSRIs: HR=1.24; 95%CI, 1.21-1.27; TCAs: HR=1.23; 95%CI, 1.07-1.29; other anti-depressants: HR=1.29; 95%CI, 1.24-1.35; combination of anti-depressants: HR=1.20; 95%CI, 1.13-1.27).

Conclusion: More attention is needed towards anti-depressant prescriptions in HF patients, especially in those without a clinical depression. Future research should focus on differences in patient characteristics between anti-depressant subgroups, and identify the unique pharmacological properties of individual anti-depressants, as this may be crucial in understanding the anti-depressant effects on cardiac function and mortality.

INTRODUCTION

Depression is prevalent in 15%-40% of patients with heart failure (HF) and increases the risk for mortality and rehospitalization.[1, 2] Given the assumption that treating depression in HF would improve prognosis, there has been a considerable rise in anti-depressant use in these patients over the past years.[1,3,4] Paradoxically, effectively treating depression by anti-depressant therapy does not seem to be a guarantee for successfully reducing the risk for adverse events in cardiovascular patients,[5, 6] with some studies even suggesting an increased risk for HF mortality.[3, 7] The association between anti-depressant use and cardiovascular events appears to depend on the class of anti-depressant medication[8] and may vary across different cardiovascular populations, definitions of anti-depressant use and statistical analyses used.[1]Not all studies adjusted statistically for depressive symptoms, nor examined the combined effect of anti-depressant use and depressive symptoms,[9-12] let alone include a diagnosis of clinical depression.

The two main classes of anti-depressant medication are the selective serotonin reuptake inhibitors (SSRIs) and the tricyclic anti-depressants (TCAs).[1] TCAs are known to have pharmacological properties that can precipitate life-threatening arrhythmias, increase heart rate and orthostatic hypotension and prolong QT-interval in patients with ischemic heart disease.[13] Despite these side effects only a few studies found that TCAs significantly increased the risk for cardiovascular disease,[8] ischemic heart disease[10] and myocardial infarction [9] in population-based samples, or mortality in patients with pre-existing HF.[3]

Findings on SSRIs suggest that their use in cardiac patients is relatively safe and induces only minimal cardiovascular effects, making them preferable over TCAs.[13] Two studies confirmed the safety of SSRIs by showing reduced incidence of myocardial infarction or mortality in HF patients using SSRIs.[14, 15] However, other studies found no significant difference in risk in relation to SSRI use.[4, 5, 8-12]

Hence, there is an urgent need to re-examine the prescription pattern of anti-depressants post HF diagnosis and the mortality risk associated with anti-depressant use in large cohorts of HF patients in order to optimize the treatment and care of these patients. The objectives of the current study were to (1) examine the prevalence of anti-depressant use in HF patients 5-years post diagnosis, (2) identify the correlates of anti-depressant use subsequent to hospital discharge, and (3) examine the relation between anti-depressant use and mortality in a large sample of HF patients. Information on HF diagnosis, use and type of

anti-depressant, and clinical diagnosis of depression were derived from the Danish registries. These registries provide a unique opportunity to track anti-depressant use over time and to examine whether the association between different anti-depressant use and mortality is similar in HF patients with and without a clinical diagnosis of depression, while controlling for potential confounders.

METHODS

Data sources and study population

The Danish National Health Service provides tax-supported health care which allows access to general practitioners and hospitals, and partially reimburses prescribed drugs. Using the civil registry number, which is unique to every Danish citizen, it is possible to perform a complete linkage of all administrative population-based registries at the individual level. The Danish registries include data on socio-demographic characteristics, socio-economic status, hospitalizations, vital status, and prescribed medications. Vital status was obtained from the Danish Civil Registration System. Diagnostic information from hospital admissions are coded using the International Classification of Diseases, Tenth Revision (ICD-10), and drugs were grouped according to Anatomical Therapeutic Chemical (ATC) codes. Because of partial reimbursement of drug expenses by the healthcare system, pharmacies in Denmark are required to register all dispensed prescriptions, ensuring complete data on date of dispensing and dosage.

Study population

For this study, we obtained information from all individuals who survived their first hospitalization admission for HF between 1997 and 2010 (ICD-codes: I11.0, I50, I42, and J81). First time admission was defined as no previous admission for HF since 1978. The registry did not allow us to distinguish between HF with preserved or reduced ejection fraction. A diagnosis of clinical depression included unipolar (i.e., major depressive episode, dysthymia) depression (ICD-codes: DF30-DF39). The prevalence of clinical depression was extracted from the registry at 90 days after discharge and at 1- and 5-year follow-up.

To ensure equal time for all patients to claim prescriptions for new medications after hospitalization, we only included patients alive 90 days after discharge. This approach has been used in previous Danish studies that have included information on medication

prescriptions.[3] The observational time started 90 days after discharge (from now on referred to as 'study baseline') and followed patients at risk for all-cause mortality until maximally December 31st 2010.

Medical treatment: Cardiac and anti-depressant medication

We used the following ATC codes to identify the use of anti-depressants (N06A), beta-blockers (C07), statins (C10A), loopdiuretics (C03C), spironolactone (C03D), aspirin (B01AC06) and angiotensin-converting enzyme (ACE) inhibitors (C09). The prevalence of anti-depressant use and cardiac medication use was extracted from the registry at 90 days after discharge, and for the anti-depressants as well at 1- and 5-years follow-up.

Statistical analysis

All continuous variables were tested for normal distribution. Continuous and categorical variables were described by the presence or absence of clinical depression and/or the use of anti-depressant medication. Statistical comparisons were made between groups using the Pearson Chi-square test for categorical variables and the Student's t-test or the Mann-Whitney U test for continuous variables. In addition, a multivariate logistic regression was performed to assess associations of anti-depressant use with mortality, adjusting for age, gender, socio-economic status, days of hospitalization, comorbidity (Charlson Comorbidity Index version 9.5.12), HF severity, other cardiac medications (i.e., beta-blockers, statins, ACE-inhibitors), and clinical diagnosis of depression. To determine the severity of HF, the average daily dosage of loop diuretics in the first 90 days after discharge was calculated (group I: 0-39mg; group II: 40-80 mg; group III: 81-160 mg; group IV: >160 mg.[3] Socio-economic status was calculated using the family income 5 years before the first diagnosis of HF, divided by the number of family members. All incomes were then divided into quintiles to generate equal size income groups.

All-cause mortality was compared between HF patients with Kaplan-Meir plots and through the estimated hazard ratio from a multivariable Cox proportional hazard regression analysis based on the use of anti-depressants thereby creating 3 groups; (1) patients using no anti-depressants and having no clinical diagnosis of depression, (2) patients using anti-depressants having no clinical diagnosis of depression, and (3) patients using anti-depressants and having a clinical diagnosis of depression. Patients having clinical depression

but not on anti-depressants were removed from the analysis (n=809). For this analysis the use of anti-depressants was defined as at least 1 prescription at 90 days after discharge from the hospital. Multivariate models were fitted with the use of socio-demographic (age, gender, marital status), socio-economic and clinical variables (days of hospitalization, comorbidity, HF severity, cardiac medication). Another Cox proportional hazard regression analysis was performed examining the impact of the use of different anti-depressant groups (i.e., TCAs, SSRI, other (tetracyclic, NaSSA, SNRI) as compared to no anti-depressant use, and on the impact of different types of anti-depressants on all-cause mortality. All analyses were performed using the Stata statistical package version 11.2 (Stata Corp, College Station, Tex).

Ethics

The Danish Data Protection Agency approved the study (No.2003-54-1269). In Denmark, historical cohort studies based on data from administrative registers do not require further ethics approval.

RESULTS

Baseline characteristics

A total of 120,443 patients survived their first hospitalization for HF during the study period. Baseline characteristics of patients in the total sample and stratified according to anti-depressant use at baseline (90 days after discharge) are shown in **Table 1**. In total, 16.6% (19,348) received anti-depressants at baseline, while 83.3% (101,095) patients received no anti-depressants. Of the patients using anti-depressants, 86.7% (16,780) of the patients had no diagnosis of clinical depression but were on anti-depressant treatment, and 13.3% (2,568) of patients were diagnosed with clinical depression and were on anti-depressant treatment subsequent to discharge.

Prevalence and correlates of anti-depressant use

The prevalence of anti-depressant use at 90 days after discharge was 16.6%. At 1-year, 98,590 patients were still alive of which 21% (20,802) patients received anti-depressant treatment while only 2% (1,972) of these patients also had a diagnosis of clinical depression. At 5-years, 37,813 patients were still alive of which 28.9% (12,083) received anti-depressant treatment while only 1% (452) of these patients also had a diagnosis of clinical depression. In

the multivariate logistic regression analysis, female gender, older age, higher socio-economic status, more comorbidities, increased use of statin, spironolactone and aspirin, a lower use of beta-blockers and ACE-inhibitors, increase in hospitalization days, greater HF severity and a diagnosis of clinical depression were independently associated with anti-depressant use subsequent to discharge **(Table 2)**.

Incidence of mortality during the follow-up period

The median follow-up duration was 2.9 years (interquartile range 1.1-5.6 years). During this period, 61.1% (61,800) of patients died in the group not using anti-antidepressants, 70.3% (11,801) died in the group using anti-depressants, and 71.3% (21,830) patients died in the group with clinical depression and using anti-depressants. The 1-, 3- and 5- year crude mortality rates were 19.0%, 49.3% and 69.8%.

Clinical depression, anti-depressant use and all-cause mortality

Univariate Cox proportional hazard regression analysis showed that patients using anti-depressants without clinical depression (HR: 1.45; 95%CI, 1.43-1.48, p<.001) and patients using anti-depressants with clinical depression (HR: 1.68; 95%CI, 1.60-1.76, p<.001) had a greater risk of all-cause mortality in comparison to HF patients not using anti-depressants and no clinical depression **(Figure 1)**. In multivariate Cox proportional hazard analyses, patients using anti-depressants, with or without clinical depression, had a significantly higher risk for all-cause mortality (ps<.001) after adjustment for socio-demographic and clinical variables **(Table 3)**. Also female gender, older age, greater HF severity and more comorbidities were significantly associated with a higher all-cause mortality risk (all ps<.001).

Anti-depressant groups and all-cause mortality

In order to examine whether group of anti-depressant (i.e., TCA, SSRI, other (tetracyclic, NaSSA, SNRI) was associated with a differential risk for all-cause mortality, a univariate Cox proportional regression hazard analysis was performed for patients using anti-depressants, stratified by anti-depressant group, using no anti-depressant use as the reference category in relation to all-cause mortality.

Table 1: Baseline characteristics for the total sample and stratified according to anti-depressant use at baseline (90 days after discharge)

	Total sample	No antidepressant use	Antidepressant use		p-value
	N=120,443	n=101,095	n=19,348		
			No depression	Depression	
			n=16,780	n=2,568	
Age (mean, SD)	73.5±13.6	73.0±14.6	74.0±12.3	77.3±10.8	**<.001**
Sex, males	64,342 (53.4%)	56,502 (55.9%)	6,950 (41.4%)	1,210 (35.8%)	**<.001**
Socio-economic status[o]					**<.001**
1	22,409 (18.7%)	19,015 (19.0%)	3,002 (17.9%)	392 (15.3%)	
2	22,812 (19.1%)	18,688 (18.6%)	3,518 (21.0%)	606 (23.6%)	
3	23,453 (19.6%)	19,008 (18.9%)	3,793 (22.6%)	652 (25.4%)	
4	24,398 (20.4%)	20,293 (20.2%)	3,557 (21.2%)	548 (21.3%)	
5	26,575 (22.2%)	23,302 (23.2%)	2,903 (17.3%)	370 (14.4%)	
HF Severity group [oo]					**<.001**
I	45,159 (37.5%)	38,694 (38.3%)	5,558 (33.1%)	907 (35.3%)	
II	31,249 (26.0%)	26,778 (26.5%)	3,931 (23.4%)	504 (21.0%)	
III	22,578 (18.7%)	18,460 (18.3%)	3,576 (21.3%)	542 (21.1%)	
IV	21,457 (17.8%)	17,163 (17.0%)	3,715 (22.1%)	579 (22.6%)	
Medical treatment after discharge					
Beta-blockers	50,837 (42.2%)	43,864 (43.4%)	6,206 (37.0%)	767 (29.9%)	**<.001**
Statins	28,575 (23.7%)	24,238 (24.0%)	3,799 (22.6%)	538 (21.0%)	**<.001**

ACE-inhibitors	63,593 (52.8%)	54,578 (54.0%)	7,981 (47.5%)	1,034 (40.3%)	**<.001**
Spironolactone	26,369 (21.9%)	22,080 (21.8%)	3,799 (22.6%)	490 (19.1%)	**<.001**
Aspirin	54,890 (45.6%)	45,686 (45.2%)	8,000 (47.7%)	1,204 (46.9%)	**<.001**
Comorbidity and history					
Myocardial infarction	30,454 (25.3%)	25,887 (25.4%)	4,155 (24.8%)	611 (23.8%)	.04
Ischemic heart disease	39,690 (32.9%)	33,695 (33.0%)	5,541 (33.0%)	806 (31.4%)	.23
Charlson Comorbidity Index					
0	56,889 (47.2%)	50,246 (49.7%)	5,974 (35.6%)	669 (26.1%)	**<.001**
1	30,321 (25.2%)	24,753 (24.5%)	4,784 (28.5%)	784 (30.5%)	
2	13,651 (11.3%)	10,820 (10.7%)	2,393 (14.3%)	438 (17.1%)	
3	9,421 (7.7%)	7,425 (7.3%)	1,531 (9.1%)	258 (10.1%)	
4	5,137 (4.3%)	3,891 (3.9%)	1,034 (6.2%)	212 (8.3%)	
≥5	5,231 (4.4%)	4,960 (3.9%)	1,064 (6.3%)	207 (8.1%)	
Hospitalization (days, mean, SD)	46.0±85.5	38.0±73.0	57.5±100.1	41.4±76.3	**<.001**

Data are represented as mean±SD or n (%)

p-values indicate the difference between the 3 groups (i.e. no anti-depressant use, anti-depressant use with clinical depression and anti-depressant use without clinical depression)

[oo]According to average daily dosage of loop diuretic (furosemide) in the first 90 days after discharge (group 1, 0-39 mg; group 2, 40-80 mg; group 3, 81-160 mg; group 4, >160mg

Table 2: Associates of anti-depressant use at baseline (90 days after discharge)

	OR	95% CI	p-value
Sex (males)	.59	.57 - .61	**<.001**
Age	1.01	1.00 - 1.02	**<.001**
Socio-economic status	1.03	1.01 - 1.04	**<.001**
Ischemic etiology	1.00	.97- 1.04	.86
HF severity	1.10	1.09 - 1.12	**<.001**
Beta-blockers	.83	.80 - .86	**<.001**
ACE-inhibitors	.87	.84 - .90	**<.001**
Spironolactone	1.07	1.03 - 1.11	**<.001**
Statins	1.05	1.00 - 1.09	**.028**
Aspirin	1.15	1.09 - 1.19	**<.001**
Hospitalization days	.99	.99 - 1.00	**<.001**
Comorbidity*	1.18	1.16 – 1.19	**<.001**
Clinical depression	4.03	3.87 - 4.20	**<.001**

**The comorbidity (index) was entered as a nominal variable (see Table 1)*
**n=120,453 due to missing data on predictor variables*

Use of SSRIs (HR: 1.53; 1.49-1.56, p<.001), TCAs (HR: 1.18; 1.12-1.24, p<.001), other anti-depressants (HR: 1.50; 1.44-1.56, p<.001) and a combination of anti-depressants (HR: 1.57; 1.49-1.67, p<.001) was associated with an increased all-cause mortality risk compared to no anti-depressant use **(Figure 2)**. In adjusted analysis, there remained a significant increased all-cause mortality risk for all anti-depressant groups (SSRIs, TCAs, other anti-depressants, combination of anti-depressants; p<.01) **(Table 4)**.

A similar analysis was performed within the group of anti-depressant users only (n=19,348), with SSRI used as reference category. In univariate analysis, use of TCA (HR: 0.86; 0.82-0.89, p<.001), other anti-depressants (HR: 0.86; 0.84-0.89, p<.001) and a combination of anti-depressants (HR: 0.81; 0.79-0.84, p<.001) were associated with a lower all-cause mortality risk compared to SSRI use. In adjusted analysis, the use of TCAs remained associated with a lower all-cause mortality risk compared to SSRI use (p<.001), but not the use of other anti-depressants (p=.18) nor a combination of anti-depressants (p=.45) **(Figure 3)**.

Anti-depressant type and all-cause mortality

Analyses of individual anti-depressants showed that prescriptions of the SSRIs fluoxetine (HR: 1.13; 1.03-1.24, p=.01), sertraline (HR: 1.17; 1.11-1.24, p<.001), citalopram (HR: 1.20; 1.17-1.23, p<.001) and escitalopram (HR: 1.28; 1.19-1.37, p<.001) at baseline were associated with an increased all-cause mortality risk **(Table 5)**. Similar results were found for the TCAs nortriptyline (HR: 1.16; 1.04-1.28, p=.005) and amitriptyline (HR: 1.14; 1.06-1.21, p<.001), the SNRIs venlafaxine (HR: 1.16; 1.07-1.25, p<.001) and duloxetine (HR: 1.39; 1.05-1.85, p=.02) and the NaSSA mirtazapine (HR: 1.21; 1.16-1.27, p<.001).

DISCUSSION

To our knowledge, this is the first large-scale study using national registry data to examine the prevalence of anti-depressant use during 5-years follow-up and the relationship between anti-depressant use and all-cause mortality in HF patients taking into account a clinical diagnosis of depression and stratifying analyses by anti-depressant group and type. We found a relatively high prevalence of anti-depressant use at baseline, which increased during the 5 years of follow-up, as was also found in a previous study.[5] In multivariate regression analyses the prescription of anti-depressants was especially associated with a diagnosis of clinical depression (OR=4.03), but also with older age, female sex, a higher severity of HF, more comorbidity, a longer duration of hospitalization after discharge and less use of cardiac medication. A combination of anti-depressant use and clinical depression subsequent to hospitalization for HF had no additive effect on the risk for all-cause mortality (HR: 1.25; 1.17-1.27), after adjustment for socio-demographic and clinical variables, compared to anti-depressant use without a diagnosis of clinical depression (HR: 1.22; 1.22-1.27). This could indicate that anti-depressant use is a proxy for unregistered (sub)clinical depression or that anti-depressant use *per se* could be responsible for the increase in all-cause mortality risk. In addition, the group of anti-depressant users without clinical depression might have been prescribed anti-depressants for other types of illnesses such as fibromyalgia or anxiety (SSRI), or diabetic neuropathy (TCA).

No previous studies have examined the combined effect of clinical depression and anti-depressant use, and studies which have investigated the separate risk of anti-depressant use *or* depression found a wide variability of associated risk.[4,5,9,10,16,17] Despite these differences,

the majority of studies found a significant increased mortality risk for both anti-depressant use[4,7,9,10,16,17] and clinical depression,[4,5,17] separately. Some studies could not distinguish the specific effect on mortality of the anti-depressants under investigation in comparison to the effect on mortality caused by the disease (i.e. depression) itself as they did not correct for depression.[1, 9, 10] Other studies examined the prevalence of depression by means of self-reported questionnaires, such as the Beck Depression Inventory (BDI) and the Geriatric Depression Scale.[4,5,17] The prevalence rates of depression in these studies were much higher as compared to the prevalence of clinical depression that we found in the current study (20-30% versus 3%, respectively), suggesting a discrepancy in the identification of depression in HF patients. Freedland et al. found that only 55% of the patients scoring in the depressed range on the BDI had clinically significant depression according to the Diagnostic Interview Schedule, and 16% of patients classified as non-depressed on the BDI were depressed according to the Diagnostic Interview Schedule despite the strong association between the BDI and the classifications of the Diagnostic and Statistical Manual of Mental Disorders.[18] Beside the differences in the assessment of depression, there were also differences in the time of assessment, as they asked patients to complete depression measures during hospitalization. Furthermore, it could be that depression which is diagnosed in primary care is not always registered as clinical depression in the patient registry, Overall, this makes it difficult to directly compare the findings.

Subgroup analyses of anti-depressants showed that use of SSRIs, TCAs, SNRIs, other anti-depressants or a combination of anti-depressants at baseline significantly increased the risk for all-cause mortality in this cohort of HF patients, even after correction for clinical depression. Although confounding by indication, in which the higher mortality risk is induced by the depression itself, cannot be ruled out the use of anti-depressants *per se* could also induce higher mortality risk through pharmacological, physiological or behavioral mechanism. TCAs, SSRI, SNRIs and other anti-depressants may have some pharmacological characteristics that are raising the mortality risk.[13] Anti-depressants have found to precipitate life-threatening arrhythmias, prolong the QT-interval and cause toxicity by drug-drug interactions.[13] There have also been found adverse physiological effects of anti-depressant us, for example on heart rate variability, sympathetic control, hypertension and inflammation.[3, 19-22] Alternatively, the elevated mortality risk could be explained by residual

confounding due to unmeasured or unknown factors, such as poor self-care. The use of SSRIs has been associated with increased risk of non-adherence to evidence-based pharmacotherapy in HF, which could explain the adverse clinical outcomes in patients on SSRIs. Equally, it is plausible that a subset of patients suffers from treatment-resistant depression, in which the anti-depressant is not capable of reducing the depressive symptoms sufficiently to decrease the mortality risk.[23]

These results, however, are surprising when compared to the findings of other studies that found no significant effect of SSRI use in adjusted analyses on mortality,[4,5,8-12] or even a significant decrease in the risk of mortality.[14,15] Furthermore, as two large randomized clinical trials that enrolled patients with coronary artery disease (i.e., Sertraline Against Depression and Heart Disease in Chronic Heart Failure SADHART and the Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy trial) found no safety issues with SSRI use an explanation for this finding is lacking.[6] These differences in findings might be attributed to methodological differences between studies including the length of follow-up.

Studies on TCAs also show mixed findings, with one study on post MI patients finding a lower but non-significant risk for mortality[15] while other studies found no significant increase in the risk for mortality, first time MI or ischemic heart disease.[5,8, 10, 11] For the group of other anti-depressants, only the study by Monster et al. found a protective effect in relation to the risk of MI,[12] with most other studies finding no significant difference in risk of use of other anti-depressants in relation to MI,[11, 15] ischemic heart disease[10] or mortality.[8] When we evaluated the mortality risk stratified by type of anti-depressant, the use of TCAs was associated with a 10% reduction in mortality risk in HF patients compared to the use of SSRIs (HR: 0.90; 0.85-0.95, p<.001), but not compared to the use of other anti-depressants or a combination of anti-depressants. The results we found might be explained by a selection bias as HF patients using TCAs are significantly younger, more often female, had a lower SES and more comorbidity although they were not significantly different with respect to disease severity (i.e. based on loopdiuretic use). However, it could be that there are unmeasured cardiac risk characteristics which may add to the selection bias between TCA and SSRI users.

Table 3: Association between clinical depression, anti-depressant use (at 90 days) and all-cause mortality (multivariate Cox proportional hazard analysis)*

Variables	All-cause mortality		
	HR	**95% CI**	**p-value**
Group			
Anti-depressants, no depression	1.25	1.22 – 1.27	**<.001**
Anti-depressants, depression	1.21	1.17 – 1.27	**<.001**
Sex	1.27	1.25 – 1.29	**<.001**
Age	1.05	1.04 – 1.05	**<.001**
Socio-economic status‡			
2	1.02	.99 – 1.04	.12
3	1.03	1.01 – 1.06	**.002**
4	.99	.96 – 1.01	.27
5	.86	.84 – .88	**<.001**
Etiology	1.01	.99 – 1.02	.37
HF severity‡			
II	1.12	1.09 – 1.14	**<.001**
III	1.33	1.30 – 1.36	**<.001**
IV	1.66	1.63 – 1.70	**<.001**
Beta-blockers	.82	.81 - .84	**<.001**
ACE-inhibitors	.90	.80 - .91	**<.001**
Spironolactone	1.12	1.10 – 1.14	**<.001**
Statins	.78	.76 - .79	**<.001**
Aspirin	1.00	.99 – 1.02	.39
Hospitalization days	1.00	.99 - 1.00	**<.001**
Comorbidity‡†			
1	1.36	1.34 – 1.38	**<.001**
2	1.58	1.54 – 1.61	**<.001**
3	1.68	1.64 – 1.73	**<.001**
4	1.99	1.92 – 2.03	**<.001**
≥5	2.20	2.12 – 2.27	**<.001**

***** *Reference group is no anti-depressants, no depression group.*

†n=120,453 due to missing data on predictor variables

‡ reference group is lowest group (socio-economic status=1, HF severity=1 and comorbidity=0)

Previous findings on the effect of individual anti-depressants on the risk of mortality in HF patients were based on the use of anti-depressants at any time during follow-up, and could therefore create discrepancies in relation to the outcomes of our study. Overall, the individual anti-depressants were found to have similar risk estimates for mortality in our cohort. We found that the use of fluoxetine, sertraline, citalopram and escitalopram subsequent to discharge leads to a higher risk of all-cause mortality in HF patients. Diez-Quevedo et al. found similar results for fluoxetine, but found no significant difference in risk for sertraline and escitalopram and even a tendency towards a lower mortality risk for citalopram.[5] Also the TCAs nortriptyline and amitriptyline, the SNRIs venlafaxine and duloxetine and the NaSSA mirtazapine showed a significant higher risk for mortality in our cohort. Except for nortriptyline, these individual anti-depressants were also examined in previous studies in which no significant difference in risk on mortality was found.[5, 10]

Limitations

The results of the current study should be interpreted with the following limitations in mind. The main limitation is inherited in the observational nature of the study and lack of information on clinical variables, e.g. left ventricular ejection fraction, New York Heart Association (NYHA) functional classification, smoking, alcohol consumption, body mass index and use of psychotherapy. Furthermore, there was a large discrepancy between the number of patients receiving anti-depressants in comparison to the number of patients having a clinical depression. It could be that depression was diagnosed in primary care and therefore not registered in the patient registry, therefore prescription of anti-depressants could be a proxy for (sub)clinical depression. We do not know anything about those who have undiagnosed depression and not receive treatment. Exposure to anti-depressants was measured only once (i.e., at 90 days post HF diagnosis), with the risk that study results could have been biased towards the null because a patient's exposure to medication may change over time. This approach was chosen as we did not obtain information on the duration of anti-depressant treatment use nor on the dosage. Furthermore, recorded prescriptions of anti-depressants are not equivalent to compliance with treatment.

Table 4: Association between type of anti-depressant (at 90 days) and all-cause mortality (multivariate Cox proportional regression hazard analysis)*

Variables	All-cause mortality		
	HR	**95% CI**	**p-value**
Any SSRI	1.24	1.21 – 1.27	**<.001**
Any TCA	1.23	1.07 – 1.19	**<.001**
Any other anti-depressant (SNRI, NaSSA, tetracylic)	1.29	1.24 – 1.35	**<.001**
Combination of anti-depressants	1.20	1.13 – 1.27	**<.001**

**Reference group is no anti-depressant use; n=120,453 due to missing data for predictor variables*

**Analysis controlled for other variables: age, sex, socio-economic status, etiology, HF severity, comorbidity, statin, beta blocker, ACE inhibitor, spironolactone, aspirin, hospitalization (days), diagnosis of clinical depression)*

CONCLUSION

In the current study, we found a high prevalence of anti-depressant use in HF patients, with and without a diagnosis of clinical depression, subsequent to hospital discharge. Use of anti-depressants increased over time after a diagnosis of HF and use of anti-depressants after hospital discharge was significantly associated with a higher all-cause mortality risk, even when adjusting for socio-demographic and clinical variables and diagnosis of depression. These results argue for more attention towards anti-depressant prescriptions in HF patients, especially in those without a clinical depression. Future research should also focus on differences in patient characteristics between the anti-depressant subgroups, and identify the unique pharmacological properties of individual anti-depressants, as this may be crucial in understanding the anti-depressant effects on cardiac function and mortality.

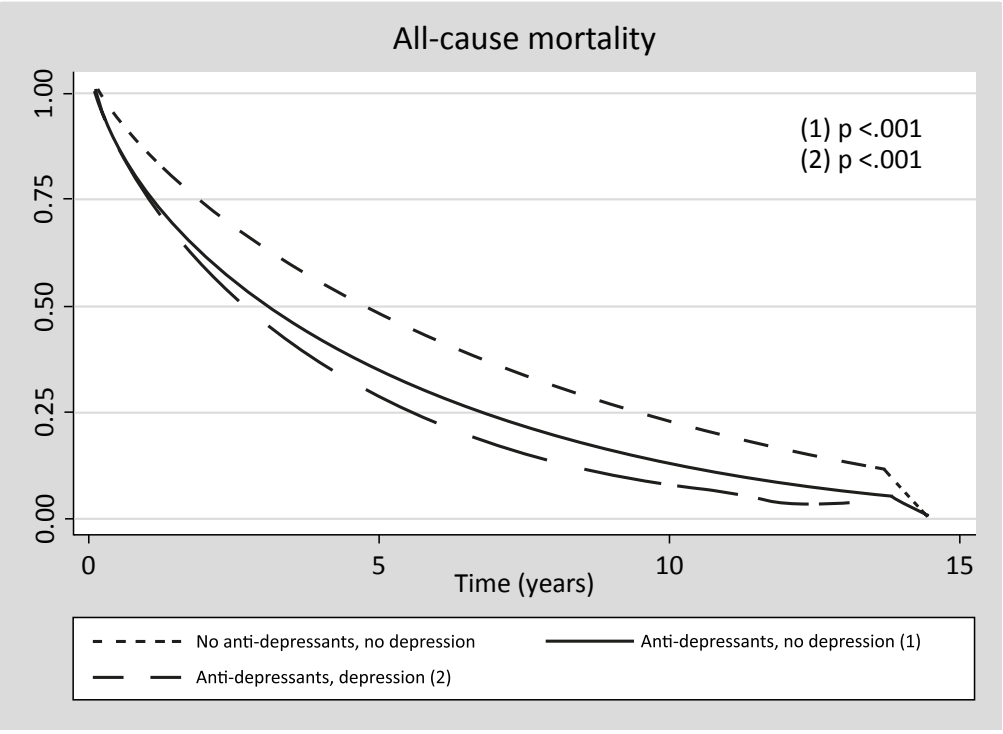
Table 5: Anti-depressant use differentiated by type in relation to all-cause mortality (n=120,443)*

Variables	Number of patients (%)	All-cause mortality		
Anti-depressant use at 90 days		**HR**	**95% CI**	**p-value**
SSRIs				
Fluoxetine	622 (0.5%)	1.13	1.03 – 1.24	**.01**
Paroxetine	570 (0.5%)	1.08	.98 – 1.20	.12
Sertraline	1,633 (1.4%)	1.17	1.11 – 1.24	**<.001**
Citalopram	9,372 (7.7%)	1.20	1.17 – 1.23	**<.001**
Escitalopram	1,551 (1.3%)	1.28	1.19 – 1.37	**<.001**
TCAs				
Nortriptyline	556 (0.5%)	1.16	1.04 – 1.28	**.005**
Amitriptyline	1,366 (1.1%)	1.14	1.06 – 1.21	**<.001**
Imipramine	289 (0.3%)	1.04	.90 - 1.21	.06
Dosulepine	53 (0.05%)	.95	.68 – 1.32	.74
Tetracyclics				
Mianserine	26 (0.02%)	.98	.63 - 1.54	.93
SNRIs				
Venlafaxine	1034 (0.9%)	1.16	1.07 - 1.25	**<.001**
Duloxetine	155 (0.1%)	1.39	1.05 - 1.85	**.02**
NaSSAs				
Mirtazapine	2789 (2.3%)	1.21	1.16 - .1.27	**<.001**

**Reference group is no anti-depressant use*

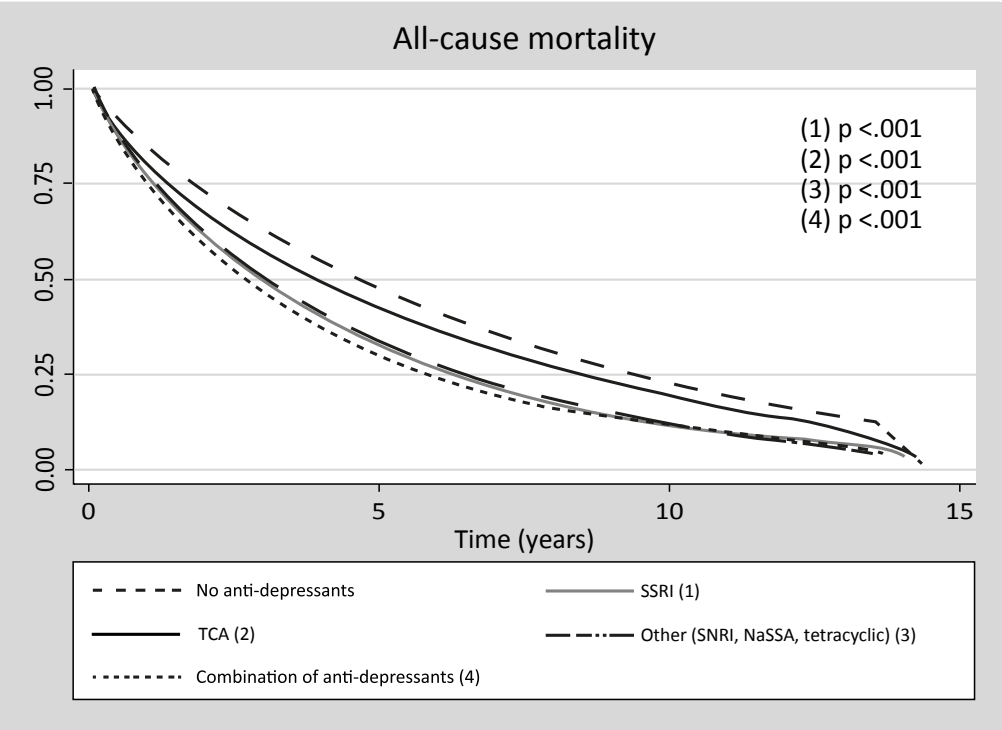
**Multivariate Cox proportional regression analysis adjusting for age, sex, socio-economic status, etiology, HF severity, comorbidity, statins, beta blockers, ACE-inhibitors, spironolactone, aspirin, hospitalization (days), and a diagnosis of clinical depression*

Figure 1: Association between clinical depression and anti-depressant use (at 90 days) and all-cause mortality (Kaplan Meier survival curve)



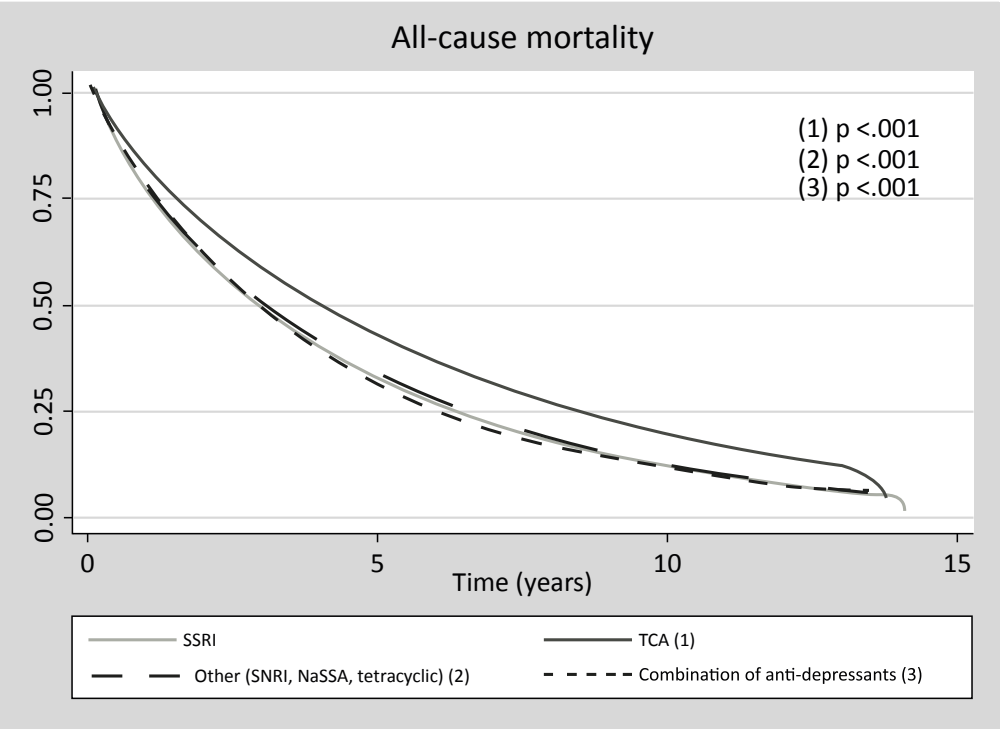
**Reference group is no anti-depressant, no depression*

Figure 2: Association between anti-depressant groups (at 90 days) and all-cause mortality (Kaplan Meier survival curve)*



**Reference group is no anti-depressants*

Figure 3: Association between anti-depressant groups (at 90 days) and all-cause mortality (Kaplan Meier survival curve)*



**Reference group is SSRI*

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CHAPTER 7

Phychological vulnerability, ventricular tachyarrhythmias and mortality in implantable cardioverter defibrillator patients: Is there a link?

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ABSTRACT

Implantable cardioverter defibrillator (ICD) therapy is the first line treatment for the prevention of sudden cardiac death (SCD). Despite demonstrated survival benefits of the ICD, predicting which patients will die suddenly from a ventricular tachyarrhythmia remains a major challenge. So far psychological factors have not been considered as potential risk markers that might enhance the prediction of SCD. We reviewed the evidence for a link between psychological vulnerability, ventricular tachyarrhythmias, and mortality, and the pathways that might explain such a link. This review demonstrates that there is cumulative evidence supporting a link between psychological vulnerability and risk of ventricular tachyarrhythmias and mortality in ICD patients independent of disease severity and other biomedical risk factors. It may be premature to include psychological factors in risk algorithms, but information on the psychological profile of the patient may help optimize the management and care of these patients in clinical practice.

The implantable cardioverter defibrillator

Implantable cardioverter defibrillator (ICD) therapy constitutes state-of-the-art and first line treatment for the prevention of sudden cardiac death (SCD).[1, 2] Key indications for ICD implantation are *secondary prevention* in patients who have survived a previous cardiac arrest without transient or reversible cause or spontaneous symptomatic sustained ventricular arrhythmia and *primary prevention* in patients considered at high risk due to a left ventricular ejection fraction (LVEF) ≤35% with ischemic or non ischemic cardiomyopathy in the absence of a history of cardiac arrest or sustained ventricular arrhythmia.[3] Risk reductions associated with ICD therapy compared to anti-arrhythmic drugs range from 37% for all-cause mortality to 57% for SCD, with ICDs being equally efficacious as primary and secondary prevention.[4]

Arrhythmias affect the electrical system of the heart, producing abnormal heart rhythms that cause the heart to pump less effectively. The ICD continuously monitors the heart rhythm, and will provide the appropriate therapy (i.e., either anti tachycardia pacing (ATP), cardioversion or a shock – up to 800 volts) to restore a normal rhythm if a life-threatening ventricular arrhythmia is detected. Generally, patients receive no warning prior to receiving a shock, and the shock itself may be uncomfortable and disturbing to the patient, with patients describing it as being similar to getting kicked in the chest by a horse.[5]

The number of patients with heart disease living with a cardiovascular implantable electronic device (CIED), such as the ICD, the bi-ventricular pacemaker providing cardiac resynchronization therapy (CRT), or the bi-ventricular pacemaker with an ICD (CRT-D), has increased substantially.[6, 7] At this time, nearly one million patients in North America and more than 800,000 in Europe have a CIED.[8] Since FDA approval and the first human implant in 1980, the complexity of the ICDs has increased considerably with novel features introduced, such as dual-chamber pacing and sensing, sophisticated algorithms to reduce the incidence of shocks, 50-fold increase in device memory, while also reducing the size of the ICD substantially (by a factor of 8).[9,10] Hence, we are dealing with an increasing population of patients with an ICD with devices that are becoming increasingly complex, although more simple devices are now also being introduced, such as the entirely subcutaneous ICD system (S-ICD®); Cameron Health Inc, San Clemente, CA, USA), which is

implanted without leads in or on the heart, thereby preserving the vasculature of the heart.[11]

Risk stratification – an unresolved challenge

Despite the demonstrated benefits of ICD therapy, predicting which patients will die suddenly from a ventricular arrhythmia remains a major challenge in clinical cardiology practice. Left ventricular dysfunction has been used for risk stratification but appears to lack sufficient sensitivity and specificity to be a good predictor of risk for SCD.[12] Other potential candidates have been pursued, such as markers of autonomic nervous system functioning (e.g. heart rate variability and baroreflex sensitivity) and microvolt T-wave alternans, but as single markers they seem to fall short of resolving the issue of optimal risk stratification.[12] Studies examining the contribution of multiple risk markers, such as the Alternans Before Cardioverter Defibrillator (ABCD) and the Risk Estimation Following Infarction Noninvasive Evaluation – ICD efficacy (REFINE-ICD) trials, show more promising results in terms of being closer to obtaining better prediction models.[13, 14] The challenge of generating algorithms that are sufficiently sensitive and specific to predict which patients are at risk of SCD is likely attributable to the complex pathology underlying SCD and the contribution of several different processes and factors interacting, including markers of arrhythmic and non-arrhythmic death.[12]

Risk stratification – is there a role for psychological factors?

The pursuit of factors that may help enhance risk stratification has mainly focused on clinical factors and physiological markers, negating the potential role of psychological factors. At this point in time, it may be too premature to suggest the inclusion of psychological factors in risk algorithms. Nevertheless, there is evidence to suggest that traumatic and psychologically taxing life events, as shown in studies examining the impact of the terrorist attack on the World Trade Center on 9/11, may increase the risk of shocks in ICD patients with a relative risk of more than two-fold.[15, 16] Although such events are rare, psychological distress and morbidity is not uncommon in ICD patients, with prevalence rates of about 20% to 25% for anxiety and depression, as reported in a recent meta-analysis.[17] Post traumatic stress disorder (PTSD) is also seen in ICD patients, although the prevalence is somewhat lower ranging from 7% to 11%.[18,19] Chronic levels of distress seem to be high in the subset of

patients who are anxious already at the time of ICD implant, with as many as 50% of patients remaining anxious 12 months post implant.[20]

Whether distress in ICD patients should be attributed to the device itself, associated therapies, such as appropriate and inappropriate shocks,[21] hardware malfunctioning,[22] underlying disease (e.g. symptomatic heart failure),[23, 24] indication for ICD implantation,[25] or the patient's pre implant psychological functioning[26] and personality disposition[27] is the subject of some debate. Irrespectively, if one out of four ICD patients suffers from significant levels of distress, we need to know whether this has consequences above and beyond its impact on quality of life [28] in this vulnerable subset of patients.

Hence, the aim of this review is (1) to examine the evidence for a link between psychological vulnerability, ventricular tachyarrhythmias, and mortality in ICD patients, and (2) to discuss the mechanisms that may be responsible for this link and implications for future research and clinical practice.

Evidence for a link between psychological vulnerability and poor clinical outcome

To date, 15 individual studies examined the association between psychological vulnerability and distress and ventricular tachyarrhythmias and mortality in ICD patients. Of all studies, seven focused on ventricular tachyarrhythmias as the outcome, while six studies focused on mortality, and two on both. **Table 1** provides an overview of these studies, with the main results summarized in the following section.

Ventricular tachyarrhythmias

In 1999, Dunbar and colleagues were the first to examine the emotional status of the patient as a potential determinant of arrhythmias in ICD patients. A higher level of total mood disturbance, as assessed with the Profile of Mood States (POMS), was associated with a greater likelihood of experiencing an arrhythmia that required ATP, cardioversion, or shock.[29] For each 10-point increase on the POMS, the chance of experiencing an arrhythmia increased by 10-20%, after controlling for factors that are traditionally associated with arrhythmia risk. More specifically, higher anxiety, fatigue, or confusion levels and a lower vigor level at one and three months post implant were associated with a higher risk of arrhythmia at three and six months, respectively. Neither anger nor depression was a significant predictor. Baseline level of mood disturbance before ICD implant did not predict

occurrence of arrhythmic events at one or three month follow-up. In 2005, Whang and colleagues showed that moderate to severe depression (Center for Epidemiologic Studies Depression (CES-D) scale ≥ 27) was associated with statistically significant increased risk of appropriate ICD shocks, after controlling for multiple potential confounders.[30] However, three other studies in ICD recipients did not support an association between patient-reported health status,[31] patient-reported[32] or physician-diagnosed[33] depression or anxiety and ventricular tachyarrhythmias. In two of these studies, the association between psychological distress and the occurrence of ICD shocks did approach statistical significance in univariable analysis (p=0.09).[32, 33]

Three studies examined the link between psychological distress and ventricular arrhythmias in ICD patients that had already received one or more shocks. By structured interviews, Fries and colleagues asked patients who had received an appropriate shock to indicate the presence and intensity of negative emotions (i.e., tension/nervousness, depression or anger) during one hour prior to a recurrent shock.[34] Based on the responses, the calculated relative risk of arrhythmia recurrence associated with mental stress was 9.5 (95% CI: 6.3-14.5). In another study, 42 ICD patients were asked to complete a diary page when they experienced a shock to retrospectively evaluate their mood state in the 15 minutes preceding the shock.[35] Results showed that moderate levels of anger were more likely during the period preceding shock than during a matched control period one week later. Other mood states (i.e., anxiety, worry, sadness, happiness, challenge, feeling in control, or interest) did not differ prior to shock compared to the control period. In 2004, Burg and colleagues showed that the patients in this sample who reported at least moderate anger in the 15 minutes preceding shocks scored significantly higher on trait anger than those who did not (p<.0001).[36] Trait anger was independently associated with anger-triggered arrhythmias (p<0.0001). Also, patients who reported at least moderate anxiety before shock scored significantly higher on trait anxiety (p<0.008). Van den Broek and colleagues showed that the clustering of anxiety at the time of implant and having a distressed (Type D) personality predicted arrhythmia, while no main effect was found for anxiety or depression.[37] Patients with a Type D personality experience a broad range of negative emotions and tend to inhibit self-expression in social interaction.[38] The two latter studies suggest that stable psychological factors increase the risk of emotion-triggered appropriate shocks in ICD patients.

In aggregate, there is some evidence that psychological distress may increase the risk for ventricular arrhythmias in ICD patients but negative studies are also available. These mixed findings might be attributed to differences in study design, the measure(s) used to assess psychological distress, sample size and variability in the follow-up period. In addition, stable psychological factors (e.g. personality) may modulate the influence of emotional distress on arrhythmias.[36, 37]

Mortality

In the past five years, studies have emerged that examined the impact of psychological vulnerability and distress on mortality in ICD patients. A sub-study of the prospective Antiarrhythmics Versus Implantable Defibrillators (AVID) trial showed that a disease-specific quality of life measurement (Quality of Life Index – Cardiac Version (QLI-CV)) was a significant predictor of all-cause mortality, even after controlling for conventional clinical risk factors including left ventricular function and symptomatic heart failure [39, 40]. However, the mental health component score of the generic 36-item Short Form health survey (SF-36) was not associated with mortality. By contrast, the Multicenter Automatic Defibrillator Implantation Trial *(*MADIT-II) showed a significant association between mental health status as assessed with the SF-12 and mortality.[31] In adjusted analyses, patients who reported psychological distress had a 39% higher risk of mortality.

Ladwig and colleagues showed that patients reporting symptoms of PTSD after ICD implantation had a three-fold higher mortality risk, even after adjusting for ICD-specific factors and for affective morbidity.[41] In another study, the risk of poor prognosis was enhanced by two-fold in patients with a Type D personality or patients with a high pre-implantation level of ICD concerns (i.e., patient concerns about the ICD giving a shock and irrespective of whether patients have actually received a shock).[42] The risk of poor prognosis increased to almost four-fold in patients with clustering of both psychological risk markers compared with patients with only one or none of these markers.[42]

In a recent cohort study with a long-term follow-up, the presence of depressive symptoms was shown to significantly increase risk for all-cause mortality in ICD patients.[43] However, depression lost its predictive value when adjusting statistically for potential confounders.[43] The association between depression and mortality was investigated further by van den Broek and colleagues, with depression also being subdivided into two symptom dimensions

(i.e., somatic symptoms and cognitive symptoms).[44] Results indicated that somatic, but not cognitive, symptoms of depression predicted mortality, independent of demographic and clinical factors. Patient-reported negative but not positive mood was also independently related to all-cause as well as cardiac-related mortality.[44] In a recent study in patients with an CRT-D, Shalaby and colleagues found that patients with a diagnosed mood disorder were at significantly higher risk of heart failure hospitalization or combined heart failure hospitalization and mortality, but not mortality alone.[33]

Thus, the majority of available studies support an association between psychological distress and mortality in ICD patients, indicating that a subset of patients is at risk of mortality despite state-of-the-art treatment due to their psychological profile. Whether psychological factors exert an independent effect on clinical outcome in ICD patients or whether their relationship with clinical outcome can be explained by other factors that are causally related to this outcome is as yet unclear.

Mechanisms linking distress to poor health outcomes

There are several plausible mechanisms that may explain the association between psychological distress and ventricular tachyarrhythmias and mortality in ICD patients. However, most of this evidence is implicit and is derived from studies that were conducted in individuals without somatic disease or in patients with general cardiovascular disease. These pathophysiological and behavioral mechanisms will be outlined in further detail below.

Autonomic nervous system dysfunction

An imbalance between the sympathetic and parasympathetic nervous systems is assumed to be one of the primary physiological mechanisms through which distress may influence overall health and predict clinical outcomes in patients with cardiovascular disease.[45] Patients with depression and anxiety tend to have impaired vagally mediated baroflex control of the heart and an increase in sympathetic tone, characterized by an increased level of norepinephrine,[46] a decrease in heart rate variability,[47,48] and abnormal heart rate-turbulence.[49] These parameters which reflect imbalance in autonomic tone have been implicated in the onset of cardiac events, including ventricular fibrillation, ventricular arrhythmias and mortality in ICD patients[35,43,50] and in patients post myocardial infaction.[49,51]

Heterogeneities in ventricular repolarization: QT-dispersion and T-wave alternans

Heterogeneities in ventricular repolarization, including QT-dispersion and T-wave alternans, have also been implicated in cardiovascular prognosis and SCD.[45] The QT-interval is the electrocardiographic representation of ventricular repolarization time, and variability in the QT-interval has been consistently linked with depression and emotional stress in patients with a myocardial infarction or acute coronary syndrome.[52,53] These findings could be explained by the use of selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants which are known to exert a proarrhythmic effect attributed to cardiac and vascular sodium, potassium and calcium channel blockage and disruption of channel protein trafficking,[54] thereby causing a prolongation of the QT-interval. However, findings on this topic are scarce, and in only one of the studies the relation between QT-interval and depression remained significant even after excluding patients on anti-depressants, but only among women.[52]

T-wave alternans is a marker of ventricular repolarization instability that may be mechanistically related to arrhythmias.[55] One study found that T-wave alternans induced by anger in a laboratory setting predicted future ventricular arrhythmias in patients with an ICD, suggesting that distress (e.g. anger) may lead to repolarization instability.[56]

Inflammation

Depression might lead to an increased activity of the hypothalamic-pituitary-adrenal axis, which results in corticotrophin hypersecretion, increased release of glucocorticoids, and elevated corticotrophin releasing hormone (CRH) activation.[57] Cortisol, which is the primary glucocorticoid in humans, and CRH have been found to stimulate pro-inflammatory cytokine release which exerts a deleterious effect on the heart due to its implication in plaque ruptures[58] and by suppressing cardiac contractility[58] while impeding cardiac remodeling.[57, 59] In addition, excess cortisol can contribute to abdominal obesity, insulin resistance, hypertension, oxidative stress, altered plasma lipoprotein metabolism and vascular tone change, which can all contribute to cardiovascular disease progression.[45]

Two studies found elevated levels of anxiety and PTSD to be independently associated with abnormal levels of acute-phase proteins and several pro-inflammatory cytokines (e.g. interleukin(IL)-6 and tumor necrosis factor(TNF)-α) in cardiac patients.[60] Also, Type D

personality was associated with higher levels of pro-inflammatory cytokines and lower levels of anti-inflammatory cytokines in patients with heart failure.[61]

Up till now, a paucity of studies have investigated the relationship between inflammatory (bio)markers and ventricular tachyarrhythmias in ICD patients. One study found no correlation between plasma levels of IL-6, TNF- α, high-sensitive C-reactive protein (hs-CRP) and brain natriuretic peptide (BNP) and ventricular arrhythmic events among stable heart failure patients having ICD's, while in another study hs-CRP was correlated with ventricular tachyarrhythmias in 121 ICD recipients over a 1-year period.[62, 63]

Platelet activation

A few studies found a link between depression and change in platelet activation, and between phobic anxiety and abnormalities in the platelet serotonin transporters and intracellular calcium levels leading to changes in the fibrinolytic system.[64] Platelets play a key role in the development of atherosclerosis, thrombosis and acute coronary syndromes,[65] thereby possibly increasing the risk for cardiac mortality in ICD patients. This effect might be attenuated by the use of SSRIs, since these have been demonstrated to reduce platelet activation by inhibiting their serotonin uptake capacity which is necessary for platelet aggregation. SSRIs may therefore also protect against the risk for new cardiovascular events.[66] However, it is not completely clear whether the normalization of platelet function after SSRI treatment is the result of a decrease in depressive symptoms or a direct effect on the platelets.[67]

Behavioral mechanisms

On the behavioral side, the primary candidate mechanisms that could explain poor health outcomes in distressed ICD patients include poor medication adherence, insufficient exercise, unhealthy lifestyle habits and the cancelling of scheduled medical appointments.[68,69] Evidence suggests that patients with depression tend to more often forget or skip their medication also after adjustment for potential confounding variables, including age, ethnicity, education, social support, and measures of cardiac disease severity,[69] thereby increasing the risk of arrhythmia's and mortality. Similarly, depression has found to be a strong determinant of all dimensions of subjective fatigue in patients with coronary artery

disease,[70] which may influence patient motivation to engage in exercise.[70] The lack of exercise may also result from anticipatory-anxiety, with ICD patients having a restricted lifestyle because of the fear of a shock.[71] Also PTSD has been associated with a higher rate of physical inactivity in terms of overall exercise and self-rated level of exercise in cardiovascular patients.[72] Due to inactivity, distressed patients may experience weight gain and be more prone to develop obesity. Weight gain and obesity can also be side effects of psychotropic drugs prescribed for affective disorders.[73] Depressed patients who have been hospitalized for cardiovascular disease are also more likely to smoke.[74] with smoking likely serving as an 'emotional painkiller'. Smoking is known to cause a restriction of the arteries, modify oxygen-dependent enzymes, increase blood pressure, diminish the amount of oxygen in the body, and reduce blood flow to the extremities.[75] Chemicals present in cigarettes lead to atherosclerosis and damage arteries and blood vessels, which eventually lead to cardiovascular disease, arrhythmogenic events or death.[75]

Furthermore, impaired cognitive focus, reduced energy, and motivation associated with depression and anxiety might affect patients' willingness to engage in self-care, to attend scheduled hospital appointments and to complete cardiac rehabilitation.[76,77] Also Type D personality has been associated with inadequate consultation behaviour among heart failure patients (i.e., consulting a physician when experiencing cardiac symptoms), increasing the risk for adverse clinical outcomes in patients with this particular personality profile.[78]

Expert commentary

There is considerable evidence that patients implanted with an ICD may be at increased risk for ventricular tachyarrhythmias and mortality due to their pre implant psychological vulnerability or post implant distress level, as shown in this review. The majority of this evidence comes from large-scale and well designed prospective studies, emphasizing that the evidence is unlikely to be spurious. Moreover, the risk associated with psychological vulnerability and distress is clinically relevant with up to a three-fold increased risk, and seems to be independent of traditional risk factors, such as left ventricular dysfunction and extent of heart failure as indicated by New York Heart Association (NYHA) functional class.[31, 37, 41] Thus, despite state-of-the-art treatment with ICD therapy for the prevention of SCD, a subset of patients die prematurely due to their psychological profile and do not benefit

optimally from their device. This should be placed in the context of the cost of the ICD, which is considerable with an average price of US$ 25,000 for the device itself.[79] Although cost-effectiveness analyses of ICD treatment as compared to anti arrhythmic drugs show that device therapy is cost-effective,[80,81] these studies did not take into account the psychological risk profile of patients.

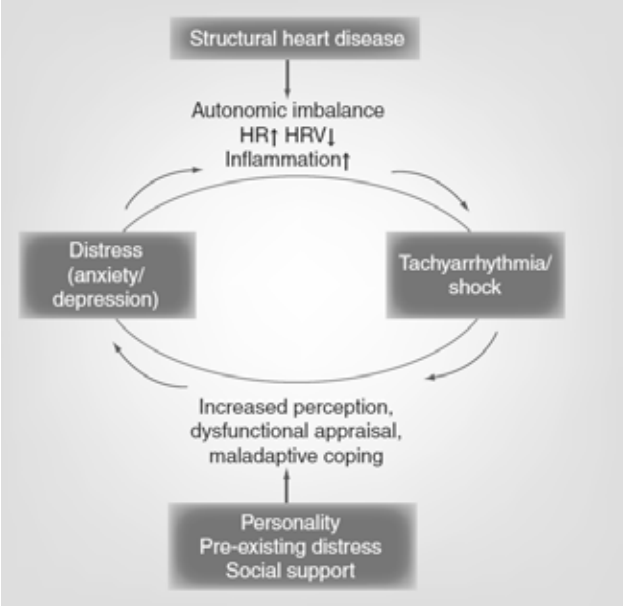
Further research in this area is warranted in order to establish whether psychological factors carry independent risk, act indirectly via physiological or behavioral pathways, or whether they can be explained by other factors. We should also explore whether psychological factors interact with demographic and clinical risk factors to enhance risk for poor clinical outcome, and whether psychological factors have a place in algorithms used for risk stratification. With this knowledge, we will be better able to manage and care for the subset of ICD patients who have an increased vulnerability for adverse clinical outcomes due to their psychological profile. Until such evidence is available, we need to acknowledge that the psychological profile of ICD patients matters in the clinical management and care, and that a vicious cycle may ensue if we do not target distress in our patients irrespective of the cause (i.e., ICD shock, underlying heart disease, pre implantation psychological profile, etc.) of that distress **(Figure 1)**.[82] Such investment seems worthwhile given the cost of the ICD but also for the sake of the well being of our patients, as it would otherwise be tantamount to ignore the considerable body of evidence from cardiovascular and behavioral medicine that shows that the body, mind and heart interact to influence health outcomes in cardiac patients.[83]

Conclusion

Cumulative evidence from large-scale prospective studies indicates that distress and psychological vulnerability may increase the risk of ventricular tachyarrhythmias and mortality in ICD patients independent of traditional clinical risk factors and despite state-of-the-art treatment with this life-saving device. Further research is warranted to disentangle whether psychological factors constitute risk factors in their own right, whether they exert indirect effects via physiological and behavioral pathways, or whether their link with prognosis can be explained by other factors. Although it may be too premature to suggest the inclusion of psychological factors in risk algorithms, information on the psychological

profile of the patient may help optimize the management and care of this subset of vulnerable ICD patients in clinical practice.

Figure 2: Supposed vicious cycle of shocks and distress*



** Braunschweig F, Boriani G, Bauer A, Hatala R, Herrmann-Lingen C, Kautzner J, Pedersen SS, Pehrson S, Ricci R, Schalij MJ. Management of patients receiving implantable cardiac defibrillator shocks: recommendations for acute and long-term patient management.Europace 2010;12(12):1673-90, by permission of Oxford University Press.*

During the course of the next five years, if we continue to invest in the patient perspective in patients with an ICD combined with evaluating potential mechanistic pathways, we will be able to document the role of the patient's psychological profile and level of post implant distress on clinical outcome and identify the subset of patients at risk for SCD. We will be more knowledgeable about the factors that determine the risk for SCD, whether it be due to the complex pathology underlying SCD, the psychological profile of the patient, or the interaction between several different processes and factors of a physiological, behavioral, and psychological nature. There is currently considerable interest in the patient perspective by policy makers, physicians and other health care professionals. This is also reflected in the

recommendations as set out by the American Institute of Medicine for the health care system of the 21st century, which should be a system that provides consistent and high-quality care that is patient-centered.[84] In these recommendations, it is stipulated that future medical treatment should fulfill the key aspects of being *safe*, *effective*, *timely*, *equitable*, *efficient* and *patient-centered*. The European Heart Rhythm Association (EHRA) - under the auspices of the European Society of Cardiology - also emphasizes the importance of the patient perspective in their mission statement: *"The EHRA mission statement is to improve the quality of life of the European population by reducing the impact of cardiac arrhythmias and reduce sudden cardiac death."* Similarly, the device industry is investing in the patient perspective by including quality of life as an endpoint when designing trials and registries to evaluate the safety and efficacy of new hardware and algorithms (e.g. to reduce appropriate and inappropriate shocks).

This holds important promise for the future well being of ICD patients and is hopefully a trend that will continue. Based on these trends, it will be interesting to see how the management and clinical care of ICD patients will evolve during the next five years also due to changes in clinical care, with more ICD patients being followed via remote monitoring. One of the important questions will be whether the subset of ICD patients with a vulnerable pre implant psychological profile or post implant distress will be detected and treated in order to preserve their well being and enhance their survival. Screening and monitoring of ICD patients for mental health issues is not yet part of standard clinical practice, but will hopefully be entered on equal footing with offering patients cardiac rehabilitation in the future. Current evidence from behavioral and psychological intervention trials in ICD patients indicate that we do have something to offer to the subset of vulnerable ICD patients in terms of reducing their distress levels and improving their well being. Even though some of these trials are plagued by methodological short comings, they show that multifactorial interventions are likely to be the most successful, including for example cognitive behavioral therapy, psycho-education about the ICD, and cardiac rehabilitation as some of the mainstay components,[85] which can if warranted be combined with pharmacological treatment. Other trials with the aim to improve to improve mental health outcomes in ICD patients are currently underway that use comprehensive and state-of-the-art techniques in behavioral medicine including e-health.[86, 87]

Key issues

- Implantable cardioverter defibrillator (ICD) therapy is the first line treatment for the primary and secondary prevention of sudden cardiac death with superior survival benefits as compared to anti-arrhythmic drugs.
- Predicting which patients will die suddenly from a ventricular tachyarrhythmia still remains a major challenge in clinical cardiology practice.
- The pursuit of factors that may help enhance risk stratification has solely focused on clinical factors and physiological factors. This despite cumulative evidence supporting a link between psychological vulnerability and the risk of VTs and mortality in ICD patients.
- Little is known about the pathways through which psychological factors may exert an influence on clinical outcome in ICD patients with both plausible physiological and behavioral pathways existing.
- Further research is warranted to establish whether psychological factors comprise risk factors or risk markers that may be attributed to other factors such as an imbalance between the sympathetic and parasympathetic nervous systems.
- It may be premature to include psychological factors in risk algorithms, but information on the psychological profile of the patient may help optimize the management and care of this subset of vulnerable ICD patients in clinical practice.

Table 1: Studies examining the link between psychological factors ventricular tachyarrhythmias and mortality

Study (year)	N mean age % men	Follow-up duration	Psychological factor(s)	Results of multivariate analyses (if available)	Covariates
Ventricular arrhythmias (appropriate ICD therapy)					
Dunbar et al. 1999 [29]	176 ICD patients 59.8±13 yrs 82% men	1, 3, 6 and 9 months	Total Mood Disturbance (POMS) (10 point increase)	1 month: NS 1-3 months: OR 1.16, 95% CI 1.03-1.32, p=0.01 3-6 months: OR 1.14, 95% CI 1.03-1.30, p=0.04 6-9 months: NS	History of cardiac arrest, history of CAD, LVEF, amiodarone, β-blockers.
Fries et al. 2002[34]	43 ICD patients presenting after appropriate shock 58±13 yrs 81% men	N/A	Mental stress defined by the presence of negative emotions (tension/nervousness, depression or anger) graded on a 4-point intensity scale during or up to a risk period of 1h before arrhythmia recurrence	RR 9.5, 95% CI 6.3-14.5	-
Lampert et al. 2002; Burg et al. 2004[35,36]	42 ICD patients that received 1 or more appropriate shocks 65±7 yrs 78.6% men	N/A	Diary with a 5-point Likert scale of intensity to evaluate levels of anger, anxiety, worry, sadness, happiness, and feelings of challenge, interest and being in control (15 minutes preceding shock)	Anger: OR 1.83, 95% CI 1.04-3.16, p<0.04 Anxiety: OR 1.51, 95% CI 0.93-.2.42, p=0.09 Worry: OR 1.16, 95% CI 0.72-1.84, p=0.54 Sadness: OR 1.22, 95% CI 0.67-2.25, p=0.52 Happiness: OR 0.87, 95% CI 0.60-1.25, p=0.44 Challenge: OR 1.24, 95% CI 0.85-1.83, p=0.27 Interest: OR 1.02, 95% CI 0.70-1.50, p=0.92	Multiple events within one single individual

Whang et al. 2005[30]	645 ICD patients (TOVA) 81.7% men	359 days (IQR 180-526)	Moderate to severe depression (CES-D≥27)	First shock: HR 3.2, 95% CI 1.1-9.9 All shocks (incl. recurrent episodes): HR 3.2, 95% CI 1.2-8.6	Age, sex, number of prior ICD discharges, time from ICD implant to study enrollment, cardiac arrest as a device indication, CAD, angina class, CHF class, LVEF, smoking, alcohol use, SSRI, ACE-inhibitors, ARBs
Piotrowicz et al. 2007[31]	1058 patients ICD or CAU 84.1% men	3 years	Mental health (SF-12) - median cut-off - per 10-unit decrease	HR 1.28, 95% CI 0.91–1.79, p=0.16 HR 1.10, 95% CI 0.94–1.29, p=0.24	Sex, NYHA class, presence of diabetes, and BMI .30 kg/m2
Dougherty et al. 2009[32]	168 ICD secondary prevention 64.1±12.3 76% men	12 months	Depression (CES-D ≥16) Anxiety (STAI ≥40)	OR 1.01, p=0.31 OR 2.82, p=0.09	-
Van den Broek et al. 2009[37]	391 ICD patients 62.3±10.4 yrs 81% men	12 months	Depression (BDI ≥10) Anxiety (STAI≥40) Type D personality (DS14)	NS NS NS Anxiety* Type D: HR 1.72, 95% CI 1.03-2.89, p=0.04	Age, sex, ICD indication, etiology, LVEF, prolonged QRS duration, ACE-inhibitors, β-blockers

Shalaby et al. 2011[33]	153 CRT-D patients 67.8±10.5 yrs 98.7% men	31.4±14.7 months	Diagnosis of mood disorder (anxiety, depression and/or PTSD)	6.1±7.0 vs. 3.3±3.5, p=0.09	Age, LVEF, etiology of cardiomyopathy, number of shocks, smoking, ECG
Mortality (all-cause)					
Piotrowicz et al. 2007[31]	1058 patients ICD or CAU (MADIT-II) 84.1% men	3 years	Mental health (SF-12) - median cut-off - Per 10-unit decrease	HR 1.39, 95% CI 1.00-1.93, p=0.05 HR 1.21, 95% CI 1.04-1.42, p=0.02	Age, sex, EF, CHF, NYHA class, blood urea nitrogen level, resting heart rate, treatment
Ladwig et al. 2008[41]	147 ICD patients (LICAD) 85% men	5.1±2.2 yrs	PTSD (upper quartile IES-R)	HR 3.45, 95% CI 1.57-7.60, p=0.002	Age, sex, survey, LVEF, CHD diagnosis, prior resuscitation, β-blockers, number of ICD shocks, time since ICD implantation, depression, anxiety, comorbidities
Steinberg et al. 2008[40]	740 patients ICD (AVID) 64±10 yrs 82% men	1.5±10 yrs	Mental health (SF-36) 46-item Patient Concerns Checklist Disease-specific QoL (QLI-CV)	NS HR 1.03, p=0.01 HR 0.95, p=0.02	Age, sex, race, index arrhythmia type (VT/VF), CHF, LVEF, β-blockers, therapy group
Pedersen et al. 2010[42]	371 ICD patients (MIDAS) 57.7±12.0 yrs 79.5% men	1.7±0.5 yrs	Type D personality High device-related concerns (ICDC ≥13)	HR 2.79, 95% CI 1.25-6.21, p=0.01 HR 2.38, 95% CI 1.06-5.34, p=0.04 Type D*high concerns: HR 3.86, 95% CI 1.64-9.10, p=0.002	Age, sex, ICD indication, etiology, shocks

Kao et al. 2010[39]	507 patients ICD (AVID) 64.85±10.81 yrs 78.3% men	12 months	General QoL – MCS (SF-36) Disease-specific QoL (QLI-CV)	OR 1.23, 95% CI 0.82–1.85, p=0.32 OR 0.48, 95% CI 0.23–.99, p=0.05	Age, race, LVEF, NYHA, history of hypertension, hyperlipidemia, HF and CABG, β-blockers, diuretics
Van den Broek et al. 2011[37]	591 ICD patients 62.7±10.1 yrs 80.7% men	1150 days (281 to 2384 days)	Negative mood (GMS) Positive mood (GMS) Depression somatic symptoms (BDI) Depression cognitive symptoms (BDI)	HR 1.03, 95% CI 1.01-1.06, p=0.002 HR 1.01, 95% CI 0.98 -1.03, p=0.61 HR 1.13, 95% CI 1.04-2.23, p=0.003 HR 0.97, 95% CI 0.91 - 1.03, p=0.29	Age, sex, relationship, indication, CAD, CRT, LVEF, diabetes, smoking, β-blockers, ACE-inhibitors, shocks
Tzeis et al. 2011[43]	236 ICD patients (LICAD) 58.6±14.0 yrs 77.8% men	6.1±2.5 yrs	Depression (HADS≥8)	NS	Sex, age, ischemic cardiomyopathy, LVEF, NYHA, shocks, diabetes, renal failure, β-blockers, surbey, employed
Shalaby et al. 2011[33]	153 CRT-D patients 67.8±10.5 yrs 98.7% men	31.4±14.7 months	Diagnosis of mood disorder (anxiety, depression and/or PTSD)	NS	Age, LVEF, etiology of cardiomyopathy, number of shocks, smoking, echocardiographic improvement

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PART THREE

Health status and psychological distress - the link with inflammation and cardiac hormones



CHAPTER 8

Association between psychological measures and brain natriuretic peptide in chronic heart failure patients

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ABSTRACT

Objective: Brain natriuretic peptide (BNP) is a promising marker for heart failure diagnosis and prognosis. Although psychological factors also influence HF (HF) prognosis, this might be attributed to confounding by BNP. Our aim was to examine the association between multiple psychological markers using a prospective study design with repeated N-terminal pro-B-type natriuretic peptide (NT-proBNP) measurements.

Design: The sample comprised 94 outpatients with systolic heart failure (80% men; mean age=62.2±9.3). The psychological markers (i.e., anxiety, depression and Type D personality), assessed with the Hospital Anxiety and Depression Scale (HADS), the Beck Depression Inventory (BDI), and the Type D Scale (DS14) were assessed only at baseline. Plasma NT-proBNP levels were measured at baseline and 9 months.

Results: The prevalence of anxiety, depression and Type D personality at baseline was 23.4% (HADS-A), 17.0% (HADS-D), 46.6% (BDI) and 21.3%, respectively. At baseline, none of the psychological risk markers were associated with NT-proBNP levels (all $p > .05$). In the subset of patients with scores on psychological risk markers both at baseline and 9 months, there was no association between anxiety ($p=0.44$), depression (HADS-D: $p= 0.90$; BDI: $p=0.85$), and Type D ($p=0.63$) with NT-proBNP levels using ANOVA for repeated measures.

Conclusions: Our findings indicate that measures frequently used in HF to assess psychological risk markers are unconfounded by NT-proBNP. Further studies are warranted that replicate these findings and examine whether psychological risk markers are independent predictors of prognosis in HF or an artifact that may be attributed to other biological or behavioral mechanisms.

INTRODUCTION

Heart failure (HF), which is typically identified by features such as dyspnea, fatigue, signs of fluid retention and cardiac remodeling, is associated with considerable physical impairments, poor quality of life and increased psychological distress.[1, 2]

Despite the availability of a wide array of laboratory and radiological tests, a diagnosis of HF may initially go unnoticed. In recent years, brain natriuretic peptide (BNP) and its N-terminal pro-hormone (NT-proBNP), have been introduced as an additional method to facilitate a diagnosis of HF. BNP, which is known as B-type natriuretic peptide, belongs to the natriuretic peptide family, which contribute to cardiovascular homeostasis by promoting natriuresis and diuresis, acting as vasodilators, and exerting antimitogenic effects on cardiovascular tissues. Increased BNP levels have been shown to be strong risk indicators for a poor prognosis, but also to be of value in guiding therapy to treat HF.[3-5]

Besides being a valuable prognostic marker for HF, evidence suggests BNP may also influence psychological distress (e.g. anxiety and depression) by affecting the corticosterone response in the hypothalamus-pituitary-adrenal gland (HPA) axis.[6] However, since psychological distress is also known as an independent risk factor for HF prognosis on its own, psychological distress might be confounded by BNP and thus be a risk marker rather than a risk factor, with the relation between distress and poor prognosis being explained by increased BNP levels.[7, 8]

A paucity of studies have examined the association between episodic and chronic psychological distress and BNP levels, with most studies being cross-sectional and examining single psychological risk markers. Of the 10 available studies,[6-14] seven were conducted in HF patients.[7, 10-13, 15] Two studies focusing on anxiety found that in patients with mild HF changes in BNP concentration were positively associated with both anxiety and state anger.[13, 15] Findings on depression[6-11, 14] were mixed. The single study that focused on the distressed (Type D) personality found no association with BNP levels.[12] Thus, the evidence regarding psychological factors and BNP and NT-proBNP is inconsistent. Knowledge of the extent to which psychological measures frequently used in HF research are associated to indicators of disease severity is important, as the prevalence of psychological symptoms may be inflated and reflect somatic disease rather than true psychological morbidity if confounding is present.

Hence, we examined the link between NT-proBNP and the continuous and dichotomized scores of a broad range of psychological risk markers (i.e., depressive symptoms, anxiety and Type D personality) using a prospective study design with measurements of NT-proBNP at baseline and at 9 months.

METHODS

Study population and design

Consecutive patients (n=94) with a diagnosis of systolic HF comprised the patient sample for the current study. Patients were recruited from four different centers, that is, Aarhus University Hospital (Skejby), Aarhus University Hospital (Aalborg), Aarhus University Hospital (Amtssygehuset), and Odense University Hospital. Patients were asked to complete a set of standardized and validated questionnaires at baseline, assessing the psychological risk markers, while NT-proBNP levels were assessed both at baseline and at 9 months. Inclusion criteria were: diagnosis of systolic heart failure, left ventricular ejection fraction (LVEF) ≤40%, and stable on HF medication within the last 1 month prior to inclusion. Patients ≥75 years of age, unable to understand and read Danish, with clinical signs of acute infection, other life-threatening diseases, cognitive impairments or psychiatric comorbidity (except for affective disorders), or a myocardial infarction within the last two months were excluded. The study was approved by the Medical Ethics Committee of all participating hospitals and was conducted in accordance with the Helsinki Declaration. All patients provided written informed consent.

Measures

Demographic and clinical variables

Information on demographic and clinical variables was obtained from the patients' medical records or from purpose-designed questions in the questionnaire. Demographic variables comprised gender, age, marital status, education, working status, smoking status and body mass index (BMI). Clinical variables included left ventricular ejection fraction (LVEF), time since HF diagnosis, etiology of HF, previous cardiac events, previous hospitalizations for HF, angina pectoris, New York Heart Association (NYHA) functional class, presence of valvular heart disease, presence of coronary artery disease (CAD), hypertension, hypercholesterolemia, diabetes, anemia, kidney disease, comorbidities, cardiac medication

(betablockers, calcium antagonists, nitrates, aspirin and other platelet-aggregation inhibitors, anticoagulants, angiotensin-converting-enzyme (ACE)-inhibitors, statins, diuretics, angiotensin-receptor blockers) and psychotropic medication. LVEF was measured using the Simpson biplane method, wall motion scoring, and eyeballing depending on the patient, the echocardiographer and the available acoustic conditions.

Anxiety and depressive symptoms

The Hospital Anxiety and Depression Scale (HADS) was developed by Zigmond and Snaith in 1983 to identify probable anxiety disorders and depression among patients in non-psychiatric hospital clinics. HADS comprises of two 7-item subscales, that is, Anxiety (HADS-A) and Depression (HADS-D).[16] Items are answered on a four-point Likert Scale from 0-3 (score range 0-21). HADS is a valid and reliable measure, with good internal consistency as demonstrated by Cronbach's α (HADS-A = .80; HADS-D = .81).[16] A score of 8 to 10 is suggestive of the presence of the respective state, while a score of 11 or higher indicates probable presence of the mood disorder.[17] In the current study, a cut-off of ≥8 was used for both subscales to indicate the presence of anxiety and depressive symptoms.[16] To prevent 'noise' from somatic disorders on the scores, all symptoms of anxiety or depression relating also to somatic disease, such as dizziness, headaches, insomnia, energy and fatigue, are excluded from the HADS, which makes it an opportune measure to use in patients with HF.[18] The HADS only takes 2 to 5 minutes to complete. It has been shown to be acceptable by the population for which it was designed.[16-18] The HADS was administered at baseline.

The Beck Depression Inventory (BDI) is a 21-item self-report questionnaire.[19] It is composed of items relating to symptoms of depression such as hopelessness and irritability, cognitions such as guilt or feelings of being punished, as well as physical symptoms such as fatigue, weight loss, and lack of interest in sex.[20] Each item on the BDI is answered on a scale from 0 to 3. A score of 0–9 indicates that a person is not depressed, 10–18 mild to moderate depression, 19–29 moderate to severe depression, while 30–63 indicates severe depression. A higher score indicates more severe depressive symptoms. For this study, we used a cut-off of ≥10.[21] The BDI can be separated into two subcomponents, that is a cognitive/affective (e.g. mood) and a somatic component (e.g. fatigue). As evidence suggests that the BDI may be confounded by indicators of somatic disease, we included the HADS not only to have a

measure of anxiety, but also to examine the extent of confounding of depression with NT-proBNP with two different depression measures.[21] The BDI was administered at baseline.

Type D personality

The Type D Scale (DS14) was used to assess the distressed (Type D) personality and its two constituent 7-item subscales, negative affectivity and social inhibition. Negative affectivity refers to the tendency to experience negative emotions, like anger, dysphoria, irritability, hostile feelings, depressed affect, and anxiety. Social inhibition refers to discomfort in social interactions, reticence and lack of social poise.[22] Items are rated on a 5-point Likert scale ranging from 0 (false) to 4 (true), with subscale scores ranging from 0-28. A cut-off of ≥10 on both subscales is used to classify patients as Type D.[22] The construct of Type D personality is stable when compared to the effect of gender on outcomes.[23] The DS14 was administered at baseline.

NT-proBNP levels

The N-terminal (NT) proBNP, the biologically inactive preprohormone of BNP, which has a longer half-life than BNP and is found in plasma was evaluated at baseline and 9 months. Blood was obtained by venipuncture under standardized conditions (after 15 min. rest – no tourniquet used) and collected in tubes containing ethylenediamine-tetraacetic acid. The blood samples were centrifugated at 2000x for 20 min. at 4°C. The plasma was then extracted and stored at -80°C prior to testing. NT-proBNP was measured using an electrochemiluminescence immunoassay (Cobas, Elecsys 2010 Systems, Roche Diagnostics Gmbh, Mannheim, Germany) according to the manufacturer's instructions. The coefficient of variation for the NT-proBNP assay was 2-5% and the analytical measurement range for NT-proBNP was 5-35,000 pg/mL.

Statistical analysis

Descriptive statistics were obtained to describe the demographic and clinical characteristics of the study sample. Student's t-test for independent samples and Pearson's correlation for parametric tests were used for examining the associations between baseline psychological risk markers and NT-proBNP at baseline and 9 months follow-up. Analysis of variance (ANOVA) with repeated measures were used to examine the associations between

dichotomized psychological risk markers assessed at baseline and NT-proBNP at baseline and 9-months follow-up. NT-proBNP levels were positively skewed and logarithmic transformations were applied prior to parametric analyses. All data were analyzed using SPSS 17.0 for Windows (SPSS Inc., Chicago, Illinois). All tests were two-tailed, and a p-value <0.05 was used to indicate statistical significance.

RESULTS

Patient characteristics

Of 190 eligible patients, 3 were omitted due to personnel error, and 65 declined participation resulting in a final response rate of 65.8% (n=122). Twenty-eight patients had either no psychological measuremen6ts or no NT-proBNP measurement and were excluded from analysis leaving 94 systolic HF patients. All study participants were outpatients at the time of recruitment. Of these patients, all (100%) had complete HADS and DS14 scores, and 76 had complete BDI scores (80.9%). The prevalence of anxiety at baseline, as measured with HADS-A, was 23.4% (22/94). The prevalence of depressive symptoms at baseline was 17.0% (16/94) with the HADS-D and 46.6% (41/88) when assessed with the BDI. Of all patients, 21.3% (20/94) had a Type D personality. Demographic, clinical and psychological baseline characteristics of the patients are shown in **Table 1**.

NT-proBNP

Prior to analyses, NT-proBNP was tested for outliers and its distribution; due to its skewed distribution, the data were transformed prior to statistical analysis using natural log. These data are presented as a median with inter-quartile range (IQR) for the untransformed data and as mean (SD) for the log transformed data. NT-proBNP measurement was missing randomly in some patients for logistic and practical reasons. In the total patient sample (n=122) patients with available NT-proBNP levels (baseline: n=94, 9 months: n=76) did not differ systematically from patients who did not have a NT-proBNP measurement (baseline: n=28, 9 months: n=46) on clinical, demographic, and psychological characteristics, except for patients without an NT-proBNP measurement being less likely to have valvular heart disease (79.2% vs. 93.8% p=0.025) and angina pectoris (66.7% vs. 84.7% p=0.043) than patients with information on their NT-proBNP. In the total sample, the median NT-proBNP levels were

927.0 pg/mL (IQR= 386-2268 pg/mL) at baseline, while at 9 months this level declined significantly to 614.0 pg/mL (IQR=231-1229 pg/mL) ($p<0.001$).

Table 1: Demographic and clinical baseline characteristics of the sample

	Total (n=94) Mean ± SD; n (%)
Demographics	
Male	75 (80)
Age (yrs)	62 ± 9
Partner	68 (72)
Secondary school and above	24 (25)
BMI	27.5 ± 5.4
Psychological	
HADS-A	5.0 ±4.5
HADS-D	4.5 ± 4.0
BDI*	10.7 ± 9.5
Type D personality	20 (21)
Clinical	
Etiology	
Ischemic heart disease	39 (42)
Cardiomyopathy	30 (32)
Other (bacterial, congenital e.g.)	15 (15)
NYHA functional class	
I/II	64 (68)
III	30 (32)
Angina pectoris	15 (16)
Hypercholesterolemia	36 (38)
Diabetes	20 (22)
Anemia	5 (4)
Kidney failure	15 (15)
LVEF	26.1 ± 6.8
Current smoker	23 (24)
Hospitalizations over 9 months	20 (22)
Medication use	
Beta blockers	91 (98)
Angiotensin-converting enzyme inhibitors	80 (86)
Angiotensin-receptor blockers (ARB)	12 (13)
Statins	48 (52)
Diuretics	76 (81)
Psychotropic medication	8 (8)

HADS-A= Hospital Anxiety and Depression Scale; BDI= Becks Depression Inventory; BMI= Body Mass Index; NYHA= New York Heart Association class; LVEF= left ventricular ejection fraction

Relationship between anxiety, depression and Type D personality and NT-proBNP levels (unadjusted analysis)

Table 2 presents the associations between the psychological risk markers (i.e., symptoms of anxiety, depression, and Type D personality), assessed at baseline, and NT-proBNP levels measured at baseline and at 9 months follow-up. Patients with Type D personality had higher NT-proBNP levels than patients without Type D at baseline and follow-up, but these differences were not statistically significant. There was almost no difference in NT-proBNP level between patients with and without anxiety and depression at baseline. The results did not change when calculating Pearson's rho with the continuous scores of the HADS-A (r=-.109, p=0.296), HADS-D (r=0.027, p=0.796), BDI (r=0.101, p=0.385) and DS14 (r=0.130, p=0.210 (SI) and r=0.013, p=0.903 (NA)) in relation to NT-proBNP at baseline and the HADS-A (r=-.065, p=0.581), HADS-D (r=-.064, p=0.586), BDI (r=0.109, p=0.445) and DS14 (r=0.085, p=0.474 (SI) and r=0.002, ρ=0.987 (NA)), in relation to NT-proBNP at follow-up. Neither of the subcomponents of the BDI at baseline (BDI_b n=86, df=1) and follow-up (BDI_f n=47, df=1) were significantly related to the NT-proBNP using the total continuous scores of the affective (BDI_b r=0.057, p=0.631; BDI_f r=0.063, p=0.670, respectively) and somatic items (BDI_b r=0.153, p=0.187; BDI_f r=0.156, p=0.275, respectively) (data not shown). Note that baseline NT-proBNP levels were negatively correlated with anxiety scores, and follow-up NT-proBNP levels were negatively correlated with anxiety and depression scores, as measured by the HADS-A and HADS-D.

In a secondary analysis, ANOVA with repeated measures was performed with the psychological risk markers (i.e., dichotomous scores (presence/absence) of anxiety, depressive symptoms, and Type D personality) entered as the between-subjects factors in four separate analyses with log NT-proBNP at baseline and 9 months as the outcome **(Figure 1)**. Of the total patients in the analysis (n=94), 61 (64.9%) had available data on the HADS or DS14 in combination with NT-proBNP measurements at baseline and follow-up, while 47 (50%) had available data on the BDI in combination with NT-proBNP at baseline and follow-up. The DS14 ((n=61, df=1) F=0.236; p=0.63), HADS-A ((n=61, df=1) F=0.603; p=0.44), HADS-D ((n=61, df=1) F=0.016; p=0.90), and BDI ((n=47, df=1) F=0.035; p=0.85) showed no significant interaction with NT-proBNP levels over time. Moreover, the affective ((n=47, df=1) F=0.095; p=0.45) and somatic (n=47, df=1) F=1.032; p=0.15) subcomponents of the BDI were also not

significantly related to the NT-proBNP levels, nor were the NA ((n=61, df=1) F=0.749; p=0.28) and SI (n=61, df=1) F=0.058; p=0.18) subscales of the DS-14.

Table 2: Association between baseline psychological risk markers (i.e., symptoms of anxiety and depression and Type D personality) and NT-proBNP levels (pg/ml) and log NT-proBNP at baseline and 9 months follow-up*

BASELINE	NT-proBNP Median (IQR)	log NT-proBNP Mean (SD)	p-value
HADS-A (n=94)			
Anxiety ≥8	718 ± (258-1791)	2.83 ± 0.61	
No anxiety <8	1049 ± (483-2272)	2.98 ± 0.50	0.25
HADS-D (n=94)			
Depression ≥8	931 ± (338-3232)	2.94 ± 0.65	
No depression <8	973 ± (390-2015)	2.95 ± 0.50	0.27
BDI (n=76)			
Depression ≥10	849 ± (290-3027)	2.92 ± 0.60	
No depression <10	958 ± (431-1745)	2.92 ± 0.49	0.22
DS14 (n=94)			
Type D ≥10	1204 ± (541-4940)	3.14 ± 0.60	
Non-Type D <10	886 ± (379-1642)	2.90 ± 0.50	0.24
FOLLOW-UP (9 MONTHS)			
HADS-A (n=74)			
Anxiety ≥8	480 ± (194-1199)	2.69 ± 0.57	
No anxiety <8	679 ± (232-1249)	2.73 ± 0.58	0.68
HADS-D (n=74)			
Depression ≥8	567 ± (221-997)	2.71 ± 0.59	
No depression <8	613 ± (217-1264)	2.76 ± 0.52	0.76
BDI (n=51)			
Depression ≥10	650 ± (216-1379)	2.77 ± 0.68	
No depression <10	567.0 ± (263-1248)	2.74 ± 0.43	0.85
DS14 (n=74)			
Type D ≥10	487 ± (171-1304)	2.74 ± 0.65	
Non-Type D <10	629 ± (263-1243)	2.71 ± 0.55	0.83

** T-tests were performed with natural log NT-proBNP values, p-value *<0.01 **<0.05*

Given the absence of a significant main effect between psychological risk markers and NT-proBNP in unadjusted analysis, it makes little sense to perform analysis of covariance (ANCOVA) with repeated measures to study the potential confounding of clinical and demographic characteristics on the relationship between psychological risk markers and NT-proBNP levels.

DISCUSSION

In the current study, we investigated whether common psychological risk markers in HF are confounded by disease severity, as measured by NT-proBNP. Although NT-proBNP is not a standalone marker of HF prognosis and mortality, caused mainly by the large intra-individual changes in concentrations which questions its specificity for HF, it has earned an important status of contributing to prognosis in HF patients in combination with other clinical measures. This is in part due to many HF patients having preserved LVEF but also due to the assessment of functional class being strongly influenced by symptoms of depression and having a poor inter-rater reliability.[24] Our results demonstrated that none of the psychological measures examined (i.e. HADS-A, HADS-D, BDI and DS14) were confounded by levels of NT-proBNP.

Previous studies examining the relationship between psychological risk markers and markers of HF used either BNP,[7, 10-13, 15] or NT-proBNP.[8, 9] Although these markers are not directly comparable in terms of their levels, it is possible to compare the overall results of the studies. Six out of the nine studies dedicated to this topic found a significant association between BNP or NT-proBNP and anxiety or depression. The two studies examining more than one psychological risk marker found a significant relation with anxiety *or* depression, but not both.[9, 13] In relation to depression, the studies of Gottlieb et al. and Van den Broek et al., which contained the largest sample sizes of respectively 2,322 and 4,332 (HF and non-HF) individuals, showed that BNP levels did not predict BDI scores in multivariate analyses,[10, 14] suggesting that depression and (NT-pro)BNP are independent and additive predictors that may adversely affect HF progression via independent pathophysiological pathways. The study of Pelle et al. found no relation between BNP and Type D personality nor between the Type D subdomains negative affectivity and social inhibition and BNP levels.[12] Half of these studies used a cross-sectional study design,[8-10, 12] having only a (NT-pro)BNP measurement at baseline. It has been argued in literature that the inter-individual biological variation in BNP

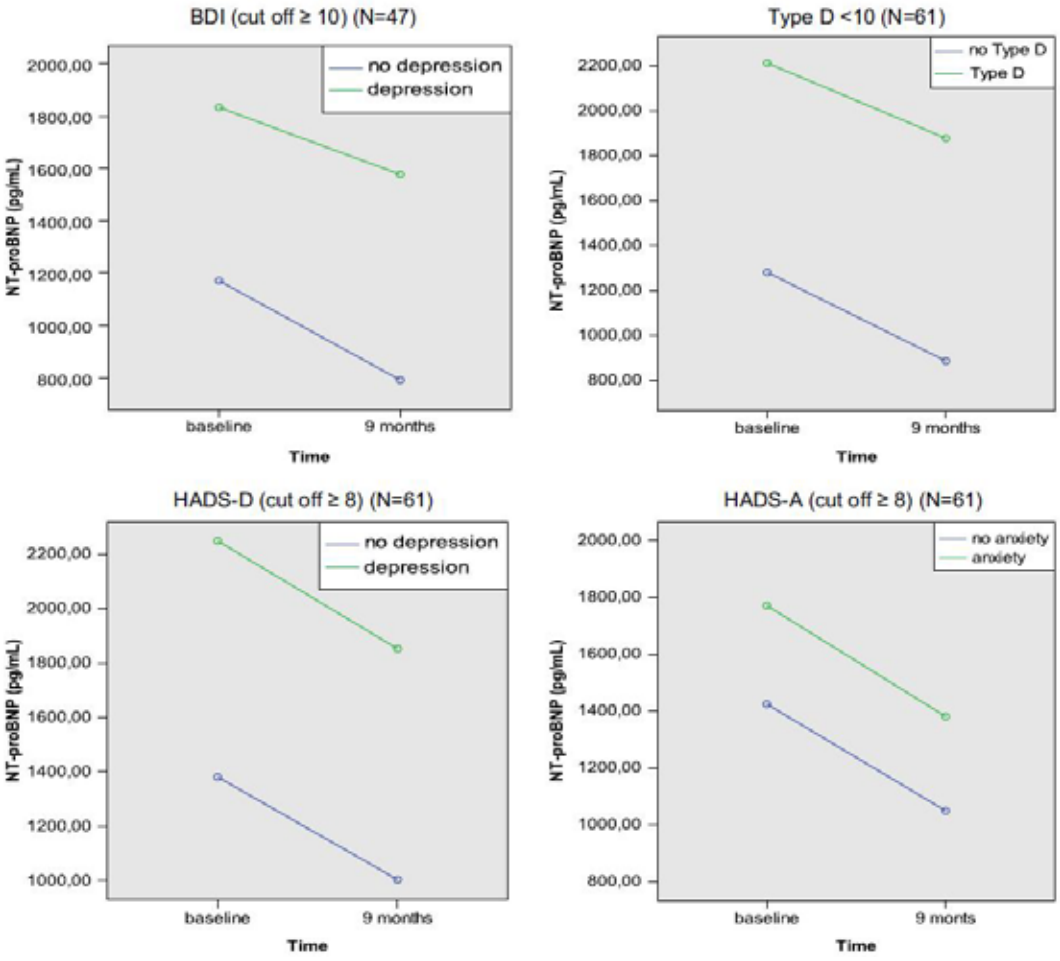
and NT-proBNP is so high that it is beneficial to increase the number of assays over time to reach a better estimate of a patients' homeostatic setpoint.[25] Hence, the prospective design of our study, with assessments of NT-proBNP both at baseline and at 9-month follow-up, and the examination of a broader range of psychological risk markers, including both episodic (i.e., anxiety and depression) and chronic (i.e., Type D personality) markers is a strength in comparison to some of the current literature on the relationship between psychological markers and potential confounding by HF disease severity.

The study of Parissis et al. reported a remarkably high prevalence of patients with depressive symptoms in their study sample (62%) using the BDI and Zung SDS.[7] In our study sample, the BDI also showed a considerably higher prevalence of depression (46.6%) than found by the HADS-D (17.0%). However, we found neither a significant relation between NT-proBNP and depressive symptoms when measured with the BDI, nor between NT-proBNP and depressive symptoms when measured with the HADS-D. In the other studies that found a significant relation between NT-proBNP and depression, analyses were performed with severely depressed patients.[8, 9, 11] Other limitations of the previous studies were the use of a self-report questionnaire for depression for which there was no designated cut-off for the severity of depression, and the inclusion of patients with less severe cardiac impairments (LVEF≥ 30%).[11, 15]

In contrast to some previous studies, we did not find a significant association between NT-proBNP levels and psychological risk markers. This indicates that the psychological measures used in the current study may not be confounded by disease severity, as measured by NT-proBNP, increasing the likelihood that they reflect true psychological morbidity rather than underlying disease severity in patients with HF. Simultaneously, this finding also points to the complexity of the relationship between psychological risk markers and HF severity, especially with respect to depression which shows the most contradicting results. It is possible that the relationship between BNP and emotional distress (e.g. depression) is dependent on the subgroup of HF patients, or on the severity of distress and symptoms. Previous studies in other HF populations show prevalence rates of depression of 21.5% (range: 19.3% - 33.6%),[26] for anxiety up to 40%,[2] and for Type D between 19 - 44% with a lower percentage in Northern and Western European country clusters (24%),[27] for Type D between 19-44% with a lower percentage in Northern and Western European country clusters (24%)[27] that are in concordance with our findings.

However, it seems prevalence rates of have been shown to vary greatly among HF subgroups, this might explain in part our null finding between psychological risk markers and NT-proBNP levels. The fact that the results found in our sample of systolic HF patients could have been dissimilar with respect to the relationship between BNP and psychological measures. An unresolved issue also pertains to the question of the 'chicken and the egg'. Although most studies indicate that the relation between emotional distress and disease severity might be bidirectional, HF is more often assumed to be the cause of emotional distress than the other way around.[10]

Figure 1: Association between psychological risk markers and NT-proBNP at baseline and at 9 months



Another important consideration is pointed out by Gottlieb et al., who suggest that emotional distress is more strongly related to subjective heart failure indices, such as NYHA functional class, than to objective indices, such as LVEF and BNP.[10] The findings by Scherer et al. concur with this notion, as there was a significant correlation between NYHA functional class and anxiety and depression, as measured by the HADS in primary care HF patients.[10, 28] Since BNP is not based on a patient's (or a clinician's) perception of disease severity, this could explain why BNP did not predict emotional distress in our study sample, as in the sample of Gottlieb et al. Furthermore, this might indicate that depression influences the perception of severity of disease to a greater extent than severe HF causing depression.[10] Taken together, it is possible that HF symptoms improve by addressing psychological problems, and that the combination of the presence of emotional distress together with BNP levels may have an additive prognostic influence in HF patients, as already mentioned by Parissis et al.[7]

The potential limitations of our study merit consideration. Since this study only analyzed the relationship between NT-proBNP and psychological measures, we cannot make any statements on whether any association between repeated NT-proBNP measures and psychological measures could directly contribute to the observed relationship between psychological measures and poor outcomes for HF. Unfortunately, we also did not have information on exercise, diet, medical adherence, heart rate variability and socio-economic status, which might have influenced our results. By excluding HF patients older than 75 years, the mean age of our sample was relatively low compared to a general HF outpatient population which could affect the generelizability of the results. Furthermore, this exclusion criteria has reduced the sample size the percentage of women within this sample. However, since the risk of cognitive deficits and the burden of filling in a package of questionnaires at several time points is expected to be more substantial with increasing age, the validity of patients' answers to the questionnaires is less likely to have been compromised.

Furthermore, for only 75% of the patient sample NT-proBNP measurements were available at baseline and 9 months. For the assessment of anxiety and depression we used a self-report measure rather than a clinical diagnostic interview. Hence, we have no information as to whether NT-proBNP is related to a clinical diagnosis of anxiety and depression. Nevertheless, even minimal symptoms, as assessed with self-report measures of depression, have been related to prognosis in cardiac populations.[29]

In conclusion, we found no relationship between any of the psychological risk markers assessed (i.e., anxiety, depressive symptoms (both with the HADS-D and the BDI), and Type D personality) and NT-proBNP levels using a prospective study design with the assessment of NT-proBNP levels both at baseline and 9-months follow-up in our sample of systolic HF outpatients. However, we have to keep in mind that until we have gained more insight into the determinants that govern het high intra-individual levels of BNP and NT-proBNP we have to be careful in drawing conclusions in relation to these outcomes with psychological measure.[25]

Although more large-scale studies are warranted to investigate and replicate BNP and its relation to anxiety, depression and Type D, these preliminary results are promising in that they show that measures frequently used in HF to assess psychological risk markers seem to be unconfounded by NT-proBNP. This suggests that screening for and treating depression in HF might have additional prognostic benefits to current standard care and management.

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CHAPTER 9

Depressive symptoms in outpatients with heart failure: Importance of inflammatory biomarkers, disease severity and personality

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ABSTRACT

Objective: Depressive symptoms are highly prevalent in heart failure (HF) patients, however the underlying etiology of depression in HF patients remains yet unclear. Hence, the goal is to examine the relative importance of inflammation, disease severity and personality as predictors of depression in HF patients.

Design: Depressive symptoms (Hospital Anxiety and Depression Scale, depression subscale) were assessed at baseline and 1 year follow-up in 268 HF patients (75.6% men; mean age =66.7±8.7). Markers of inflammation (TNFα, sTNFr1, sTNFr2, IL-6 and IL-10), disease severity (e.g. NYHA classification) and personality (Type D personality, loneliness) were assessed at baseline.

Results: At baseline, NYHA class, body mass index, educational level, Type D personality and loneliness were significantly associated with depression. Higher NYHA class (B=2.25; SE=.83), higher educational level (B=1.41; SE=.48), Type D personality (B=2.56; SE=.60) and loneliness (B= .19; SE=.05) were also independently associated with higher depression levels at one year follow-up (all p-values <0.005). Inflammation, BNP and LVEF were not related to depression over time.

Conclusions: Personality factors, but not inflammation, were independent concomitants of depressive symptoms in patients with HF. Gaining more insight into the etiology of depression in HF patients is important in order to identify potential targets for novel interventions.

INTRODUCTION

Depression has a high prevalence in heart failure (HF) populations (15%-40%) and is associated with a higher rate of mortality, rehospitalization, and general health care use among HF patients.[1-3] The underlying etiology of depression in HF patients remains yet unclear. It has been argued that physiological mechanisms and physical deterioration as a result of HF progression are the main causes of depression in HF patients.[4-6] An important physiological mechanism in HF is inflammation, which can, when being exacerbated in duration and intensity, lead to a state of depression.[7] This form of depression is generally assumed to be an inflammation-related syndrome,[7] which is characterized by somatic depressive symptoms[8] and sickness behavior.[9] In this model, bidirectional associations between depression and inflammation may contribute to the progression of HF.[10]

In case of reversed causality, depression is only a marker of greater disease severity because disease severity would cause both poor prognosis and depression. In this case depression would not be more than an epiphenomenon of the disease manifestation. However, the evidence on the relation between disease severity indices and depression is mixed.[11-14]

In addition to inflammation and disease severity, psychological vulnerability (i.e. personality, social relationships) can play a potential role in the development of depression.[15-18] Examples of the latter are Type D personality and loneliness which may influence the ability to deal with life events and to cope with one's mental and physical health challenges which is crucial to mitigate these events causing depression.[19] Type D (distressed) personality refers to individuals with elevated levels of both negative affectivity (tendency to experience negative emotions) and social inhibition (tendency to inhibit self-expression in social interactions),[20] and has been indicated in previous studies as a possible causative factors for depression in HF.[21]

Based on current knowledge we suggest the presence of three explanatory models for depression in HF, namely inflammation, disease severity and personality. Establishing the main cause of depression in HF patients is vital to identify potential targets for novel interventions in order to improve clinical outcome and quality of life. Hence, our goals were to examine the relative importance of these models as underlying etiological factors of depression in HF patients by using a cross-sectional and prospective measurement approach.

METHODS AND MATERIALS

Study population and design

Consecutive outpatients with a diagnosis of HF were recruited from the St. Elisabeth Hospital, Tilburg, the Netherlands between June 2006 and February 2009. Inclusion criteria were: LVEF ≤40%, stable on oral HF medication within one month prior to inclusion, New York Heart Association (NYHA) functional class I-III, and no hospital admissions in the month prior to inclusion. Exclusion criteria were >80 years of age, inability to understand and read Dutch, clinical signs of acute infection, active episodes of gout or arthritis, use of anti-inflammatory medication, other life-threatening diseases, myocardial infarction 2 months prior to inclusion, and cognitive impairments or psychiatric co morbidity (except for mood disorders). n=404 patients were eligible for study participation of which n=120 patients refused. Of the n=284 recruited patients, n=24 patients were non-responders and n=2 patients died at baseline leaving 268 patients eligible for analyses. Patients were asked to complete a set of questionnaires at baseline and 12 months follow-up assessing socio-demographic variables and personality risk markers. This questionnaire was returned in a stamped and pre-addressed envelope. If the questionnaire was not returned within two weeks, patients received a reminder letter. At baseline 7.8% (21/268) and at 12 months 11.2% (29/257) of the patients received at least one reminder letter for the return of the questionnaire. All questionnaires were checked for completeness. Blood samples were drawn at baseline to determine cytokine levels and clinical laboratory values (i.e. creatinine). The study was approved by the Medical Ethics Committee of the St. Elisabeth hospital in Tilburg and conducted in accordance with the most recent version of the Helsinki Declaration (2008). All patients provided written informed consent before entering the study.

Measures

Demographic and clinical variables

Demographic variables included gender, age, marital status (having a partner vs. having no partner), education (primary school vs. secondary school and above), and working status (employed/pensioner vs. unemployed). Clinical variables included etiology of HF (ischemic vs. non-ischemic), previous cardiac events (i.e., previous myocardial infarction [MI], coronary artery bypass graft [CABG] or percutaneous coronary intervention [PCI]), prescribed

medications (beta-blockers, calcium antagonists, nitrates, aspirin and other platelet-aggregation inhibitors, anticoagulants, ACE-inhibitors & ARB's, statins, diuretics and psychotropic medication), current smoking status and Body Mass Index (BMI).

Depressive symptoms

All patients filled out the Dutch version of the Hospital Anxiety and Depression Scale, depression subscale (HADS-D) to assess depressive symptoms.[22-24] The HADS-D comprises 7-items, which are answered on a four-point Likert Scale from 0-3 (range [0-21]). The HADS-D is a valid and reliable measure, with good internal consistency (Cronbach's α HADS-D = .81).[22, 23] In the current study, a cut-off of ≥8 was used to indicate the presence of clinically relevant levels of depressive symptoms, based on the optimal cut off found in large-scale studies examining the psychometric properties of the HADS.[25] The HADS has shown to be an adequate measure of depressive symptoms in cardiac patients.[26]

Inflammation

Levels of tumor necrosis factor (TNF)-α, soluble TNF receptors 1 and 2 (sTNFr1 & sTNFr2), interleukin (IL)-6 and IL-10 were obtained using standard hospital protocol. Venous blood samples were drawn and centrifuged at baseline. Blood was allowed to clot at room temperature for at least 20 minutes and centrifuged. Aliquoted serum samples were stored at -80°C in anticipation of further processing. Concentrations of IL-6 (sensitivity: 2 pg/ml), IL-10 (sensitivity: 1 pg/ml), and TNFα (sensitivity: 1.7 pg/ml), were measured using a solid-phase, enzyme labeled, chemiluminescent immunometric assay (Immulite 1000, Siemens Healthcare Diagnostics Breda, The Netherlands). Soluble tumor necrosis factor receptors (sTNFR1 and sTNFR2; sensitivity for both: 15.6 pg/ml) were measured using quantitative enzyme-linked immunosorbent assay (Hycult Biotechnology, Uden, The Netherlands). All tests were measured in accordance with the manufacturer's recommendations. The sensitivity of all tests was calculated as the mean of six zero-values plus three SDs extrapolated on the standard curve. The intra-assay variation was less than 10%, and the inter-assay variation less than 11%.

Disease severity

Disease severity variables included etiology left ventricular ejection fraction (LVEF), brain natriuretic peptide (BNP) and New York Heart Association functional class (NYHA). A comorbidity score was computed using the Charlson Comorbidity Index (CCI), which evaluates 17 different comorbidities with varying assigned weights. We used an abbreviated CCI score with the following comorbid conditions: myocardial infarction (MI), cerebrovascular disease, chronic obstructive pulmonary disease, diabetes mellitus, peripheral vascular disease, liver disease, renal failure, and any malignancy excluding metastatic tumors.[27] Renal failure was measured by calculating the glomerular filtration rate of creatinine (GFR_{creat}) using the MDRD formula, and kidney dysfunction was defined as a GFR_{creat} <60mL/min per 1.73m^2.[28,29] The comorbidity index was calculated in accordance with the original CCI in which a weight of 2 was assigned to renal failure and any malignancy, and a weight of 1 to the other comorbid conditions, depending on the relative mortality risk of each specific disease. By adding up the values assigned to each comorbid condition, a comorbidity score was calculated for each patient. Because age is a risk factor for mortality independent of the presence of comorbid conditions, we adjusted the score by adding one point to the score for each decade of life over the age of 50 at time of study entry.[27] The CCI was calculated at baseline.

Personality

For the personality model of depression we included the distressed (Type D) personality. The Type D Scale (DS14) was used to assess Type D personality and its two constituent 7-item subscales, negative affectivity and social inhibition.[30] Negative affectivity refers to the tendency to experience negative emotions (like dysphoria, irritability, hostile feelings and anxiety), and social inhibition to the tendency to inhibit self-expression in social interaction. Items are rated on a 5-point Likert scale ranging from 0 (false) to 4 (true), with subscale scores ranging from 0-28. A cut-off of ≥10 on both subscales is used to classify patients as Type D.[30] The construct of Type D personality is stable over time.[31] The DS14 was administered at baseline. The NA and SI subscales of the DS14 have good psychometric properties with Cronbach's α=.88/.86 and 3-month test–retest reliability r=.72/.82.

The social inhibition component of Type D personality might serve as an obstacle in forming stable relationships, thereby often leaving patients at higher risk of experiencing a

sense of loneliness.[32] Loneliness represents a distressful affective state in which one holds the undesired perception of having few social relationships and being isolated from others.[32] Several studies have found evidence for a relationship between loneliness and depressive symptoms,[33] but also between Type D and loneliness.[34] Based on these associations we added the 10-item University of California, Los Angeles (UCLA) Loneliness Scale, which assesses feelings of loneliness or social isolation,[35] to the personality model as an potentially important covariate. Responses of the UCLA scale may range from 1 *(never)* to 4 *(often)*. The scores ranged from 10 to 40, with higher scores indicating higher experienced levels of loneliness. This instrument has an internal consistency of 0.94.[36,37]

Statistical analyses

To compare the demographic and clinical characteristics between patients with and without cytokine measurements, *t* tests, Mann-Whitney U tests, or χ^2-tests were used depending on the measurement and variable distribution. Cytokines were positively skewed and logarithmic transformations were applied prior to parametric analyses. Due to missing variables on depression, inflammation, disease severity, personality and socio-demographic variables (≈25%) we performed a multiple imputation by using Predictive Mean Matching, (Markov Chain Monte Carlo, 20 imputations). Predictive Mean Matching is similar to the regression method except that for each missing value, it imputes a value randomly from a set of observed values whose predicted values are closest to the predicted value for the missing value from the simulated regression model. The predictive mean matching method ensures that imputed values are plausible and might be more appropriate than the regression method if the normality assumption is violated.[38]

Linear regression was used to examine inflammation markers, disease severity indices, and personality factors as associates of the depressive symptoms at baseline and 12 months follow-up. Markers of inflammation, disease severity and personality were entered in the hierarchical regression analyses using the *enter* method (Model 1). Subsequently, socio-demographic variables (age, sex, educational level, marital status, BMI) were added to the analyses thereby creating Model 2. In secondary analyses medication (statins, aspirin) was entered into the regression model to check for confounding (Model 3). To determine if inflammation markers, disease severity indices, or personality factors are predictive of depression at follow-up, also baseline depression was added to the model in the prospective

linear and logistic regression models (Model 4). The rationale for this lies in the assumption that the best predictor of subsequent depression is a prior depressive episode.[39] Therefore, one can argue that variables predicting depression at follow-up could substantially be changed or attenuated when controlling for baseline depression. The pooled estimates for the multiple imputation data were reported. The explained variance of the inflammation, disease severity and personality model, and socio-demographic variables were estimated using block entry of the variable groups and were calculated based on a method for combining R square values from imputed data sets.[40] Next, logistic regression models were constructed to enhance clinical interpretation. Continuous and dichotomous depression scores were used as the dependent variables. All predictor variables were tested for colinearity. Data were analyzed using SPSS 17.0 for Windows (SPSS Inc., Chicago, Illinois). All tests were two-tailed, and a p-value<0.05 was used to indicate statistical significance.

RESULTS

Patient characteristics

The mean age of the 268 patients was 66.7±8.7 year, 203 patients (75.6%) were men. Of all patients, 21.7% (58/268) were classified as having a Type D personality. Further information on the demographic, clinical and psychological baseline characteristics of the patients are shown in **Table 1**. Included (n=268) and non-included (n=26) patients did not differ on any socio-demographic, clinical or personality variables.

The prevalence of clinically significant depressive symptoms (HADS-D≥8) was 28% (80/268) at baseline and 29% (75/257) at 12 month follow-up. The mean HADS-D score was 4.9 (±4.0) at baseline, and 5.0 (±3.8) at follow-up. About half of the patients (141/257=66%) was neither depressed at baseline nor follow-up, 7% (17/257) of the patients were only depressed at baseline, 8% (19/257) of the patients were only depressed at 12 months follow-up and 21% (51/257) of the patients were depressed at baseline and 12 months follow-up**.** The proportion of patients with depression at baseline (n=80) were significantly higher educated (51% vs. 28%, p<.001), had more often NYHA functional class III (18% vs. 7%, p=.008), a (biventricular) pacemaker (22% vs. 11%, p<.001), kidney failure (45% vs. 27%, p=.007), a Type D personality (46% vs. 13%, p<.001) and were prescribed less diuretics compared to non-depressed patients (n=188). Depressed and non-depressed patient did not differ significantly on any other socio-demographic or clinical characteristics**.**

Table 1: Baseline and follow-up patient characteristics

	Total (n=268) n (%); mean ± SD
Socio-demographic characteristics	
Sex (% male)	202 (76%)
Age (mean ± SD)	66.7 ±8.7 years
Partner	205 (73%)
Educational level	
Primary school	167 (64%)
Secondary school and above	91 (36%)
Occupational status	
Employed/pensioner	43 (16%)
Unemployed	225 (84%)
Smoking	73 (22%)
BMI (mean ± SD)	28.2 ± 5.2
Disease severity	
NYHA classification	
NYHA I/II	237 (90%)
NYHA III	31 (10%)
LVEF (mean ± SD)	33.1±7.0
Ischemic etiology	175 (65%)
Previous MI	160 (60%)
Previous PCI	63 (24%)
Previous CABG	76 (29%)
Previous CVA	20 (8%)
Previous TIA	19 (7%)
BNP (pmol/L)	69.1±117.9
Intervention/Medication	
(Biventricular) Pacemaker	26 (10%)
ICD	40 (15%)
Beta-blockers	189 (71%)
Statines	192 (72%)
Digoxin	47 (18%)
Lisdiuretics	164 (62%)
Aspirin	96 (36%)
ACE inhibitors or ARB's	162 (67%)
Psychotropic medication	46 (17%)
Comorbidity	
COPD	50 (19%)
Kidney failure	73 (27%)
Diabetes mellitus	80 (30%)
Type I	4 (5%)
Type II	76 (95%)
Peripheral arterial disease	32 (12%)

Psychological	
HADS-D baseline (mean ± SD)	4.9±4.0
HADS-D 12 months (mean ± SD)	5.0±3.8
UCLA loneliness baseline (mean ± SD)	19.0±5.2
Type D personality (%)	58 (22%)

BMI= body mass index; LVEF= left ventricular ejection fraction; MI= myocardial infarction; PCI= Percutaneous coronary intervention; CABG= coronary artery bypass surgery; CVA= cerebrovascular accident; TIA= transient ischemic attack; ICD=implantable cardioverter defibrillator; ARB= angiotensin receptor blocker; COPD= chronic obstructive pulmonary disease

Cytokines (TNFα, sTNFr1, sTNFr2, IL-6 and IL-10)

In the total baseline sample, the median cytokine levels were: sTNFr1 6.37ng/mL (IQR=3.09ng/mL), sTNFr2 1.00ng/mL (IQR=0.97), TNFα 11.80pg/mL (IQR=5.59pg/mL), IL-6 4.13pg/mL (IQR= 3.83ng/mL) and IL10 1.83ng/mL (IQR=2.94ng/mL).

Independent correlates of depressive symptoms at baseline

In the cross-sectional adjusted model the inflammation model explained 6.0% of the total variance in baseline depression scores **(Table 2).**The disease severity model and personality model added another 6% and 42.4%, respectively, thereby explaining 54.5% of the total model variance. NYHA classification (B_1=2.43 (SE=.75), p=.001; B_2=2.38 (SE=.74), p=.001), Type D personality (B_1=2.60 (SE=.55), p<0.001; B_2=2.43 (SE=.55), p=<0.001) and loneliness (B_1=.29 (SE=.04), p<0.001; B_2=.28, p=<0.001) were independent correlates of depression before (B_1) and after (B_2) correction for socio-demographic variables. In addition, NYHA classification (B_3=2.44 (SE=.74), p=.001), Type D personality (B_3=2.42 (SE=.55), p=<.001), loneliness (B_3=.28 (SE=.04), p=<.001), educational level (B_3=1.22 (SE=.45, p=.007) and body mass index (B_3=.09 (SE=.04), p=.02) remained significant after adjustment for the medication aspirin and statins (B_3), which added 1.0% of the total variance explained.

Predictors of depressive symptoms at 12 months

Linear regression analyses were also performed with continued HADS-D scores at 12 months follow-up **(Table 3)**. The inflammation model, disease severity model and personality model explained respectively 4.5%, 6.2% and 29.6% of the model variance. NYHA classification (B_1=2.37 (SE=.85), p=.005), Type D personality (B_1=2.74 (SE=.61), p<.001) and loneliness

(B_1=.21 (SE=.05), p<.001) were significant predictors of depressive symptoms at 12 months follow-up, and remained so after correction for socio-demographic characteristics (B_2=2.33 (SE=.83), p=.005; B_2=2.58 (SE=.60), p=<.001 and B_2=.18 (SE=.05), p<.001, respectively). Higher educational level (B_2=1.45 (SE=.48), p=0.02) also appeared to be a significant predictor of depression at follow-up. Correction for aspirin and statin use added 1.2% to the total variance explained by the models and did not alter any significant results. After correction for baseline depression (B_4), which added another 16.5% to the total model, only Type D personality (B_4=1.00 (SE=.52), p=.05) and statin use (B_4=.072 (SE=.49), p=.04) were significant predictors of depression at 12 months follow-up.

Clinically relevant levels of depression

Neither the inflammation model nor the disease severity model, except for NYHA classification (OR=4.54, p=.02), was significantly associated with clinically relevant depression at 12 months in the unadjusted model. Conversely, Type D personality (OR=3.65, p=.002) and loneliness (OR=1.11, p=.008) were significant predictors of clinical levels of depression at 12 months. After correcting for socio-demographic factors, NYHA classification (OR=4.85, p=.02) was a significant predictor of depressive symptoms in addition to Type D personality (OR=4.07, p=.02), and loneliness (OR=1.09, p=.03). These findings remained relatively unchanged by adding aspirin (OR=1.41, p=.12) and statins (OR=.49, p=.34) to the model, as NYHA classification (OR=5.18, p=0.02), Type D (OR=4.24 p=.002) and loneliness (OR=1.09 p=0.03) remained significant predictors of depressive symptoms at 12 months. However, in this model also the comorbidity index became a significant predictor of depression at follow-up (OR=1.50, p=.02). The correction for baseline depression attenuated the significant predictive value of NYHA classification, Type D personality and loneliness while comorbidity index and age became significant predictors for the change in depression scores over time (OR=1.68, p=.02 and OR=2.51, p=.03, respectively) **(Figure 1).**

DISCUSSION

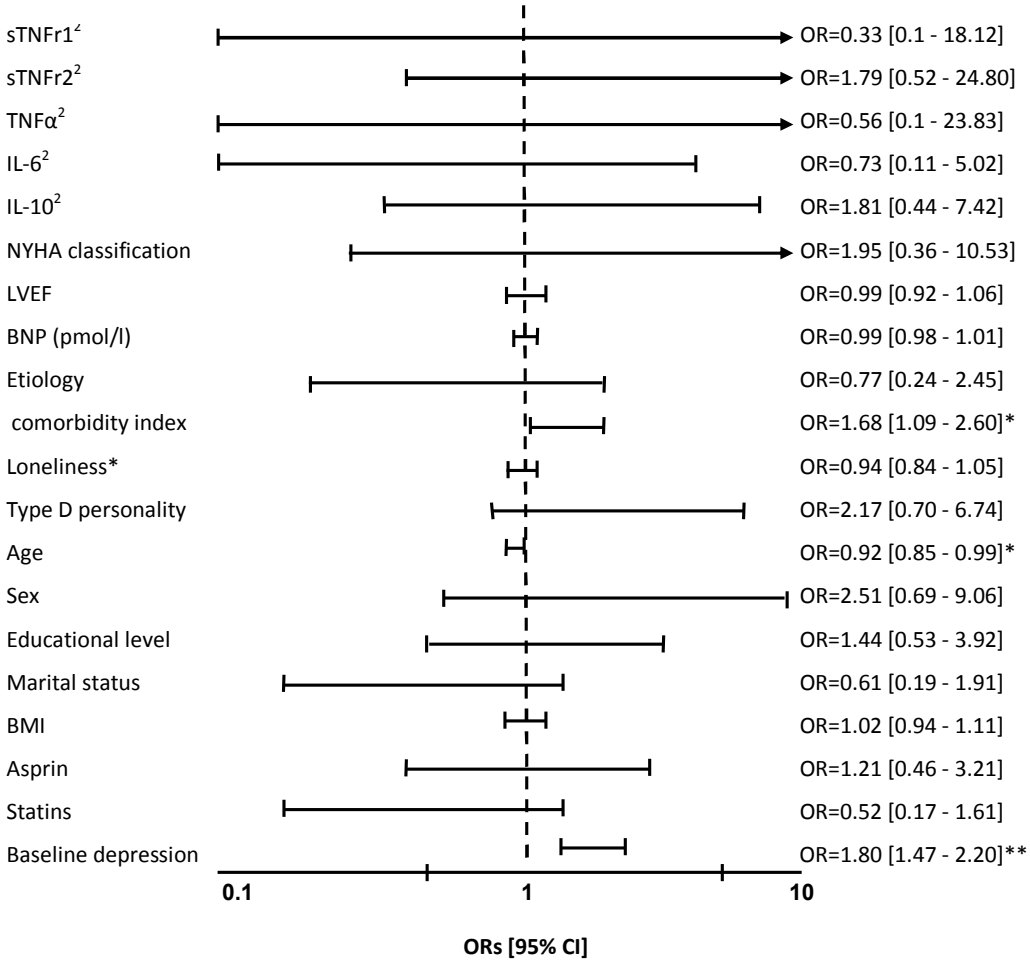
Inflammation, disease severity, and personality markers have all been implicated as potential explanatory pathways for depression in cardiac patients.[17,41] In this study personality factors (i.e. Type D personality and loneliness) predicted depressive symptoms beyond inflammation and disease severity markers, even after correcting for socio-

demographic variables (i.e. age, sex, educational level, marital status, BMI). The inflammation model, composed of five cytokines levels, did not reach a statistically significant level in the linear regression analyses. In the cross-sectional analysis NYHA classification, educational level and body mass index were the most important clinical and socio-demographic variables for predicting depression at baseline. Most of these variables lost their value as predictors of depressive symptoms in the prospective analysis, except for BMI, while Type D personality and loneliness remained statistically significant.

The role of inflammation as a predictor of depressive symptoms is based on the evidence that cytokines are involved in the stimulation of the hypothalamic corticotrophin-releasing hormone release that activates the neuroendocrine cascade of the hypothalamic-pituitary-adrenal (HPA) axis and provokes a wide range of immune functions.[10] Evidence on the role of cytokines as predictors of depression is mixed and limited to a relatively small number of studies,[5,6, 42-48] of which some used relatively small sample sizes and cross-sectional study designs.[5, 6, 42] In addition, none of these studies included personality factors.

In our sample the individual cytokines of TNFα, sTNFr1, sTNFr2, IL-6 and IL-10 were not significantly associated with depression at baseline or 1 year follow-up in the total sample. However, since depression is a heterogeneous disorder, and groups of depressed HF patients are likely to differ in psychopathology and inflammation,[9] this does not imply that in a small subset of patients a status of systemic inflammation could be the underlying cause of their depressive symptoms. The possible existence of different depression-subsets should therefore be explored in future studies with larger groups of patients suffering from a heightened systemic inflammatory state. Our findings seem consistent with the negative findings of Stewart et al.,[48] Duivis et al.,[46] and Steptoe et al.[49] using IL-6, TNFα, and other inflammatory markers. Discrepancies in findings on depression and inflammation may also be explained by the difference in study set-up (cytokine induction studies vs. (un)controlled prospective studies), the study samples or the depression assessment tools.[8, 50] About 30-50% of the patients with major depression do not show HPA axis hyperactivity,[51] making it hard to discriminate the subset of these patients that are experiencing 'sickness behavior' as a result of inflammation.[9] The association between inflammatory processes and depressive symptoms might be specific either to clinically depressed groups, to HF patients with NYHA class III-IV, or to older age samples (>70 years).[45] In fact, age is also characterized by dysregulation of inflammatory cytokines and immune senescence.[45]

Figure 1: Independent predictors of clinically elevated depression levels at 1-year follow-up[1]



[1] *Prospective analysis of dichotomous depression scores*

[2] *Entered as continuous variables; increase risk associated with one-point increase in measurement.*

**p<0.05*

***p<0.01*

Most markers of disease severity (BNP, LVEF, etiology) were not associated with depressive symptoms. Only medical NYHA classification and co morbidity were independent predictors in the linear and logistic regression model of increased depressive symptoms. In a study population with such a high prevalence of co morbidities (e.g. lipid dysfunction, diabetes and

hypertension), it can be expected that co morbidities add significantly to the burden of HF, and could therefore be important antecedents for developing depression. There was a difference in the strength of the association between depression and subjective (NYHA classification) versus objective (LVEF, BNP) disease severity measures, which coincides with the results found by Gottlieb et al.[13]

The findings of the present study support the validity of the personality model in patients with HF. Type D personality and loneliness were found to be major significant predictors of depressive symptoms, adjusting for medication and demographic and clinical covariates. Personality factors can predispose people to depression through having dysfunctional beliefs, distorted social roles, social losses, and a low rate of effective coping and positive reinforcement.[52] The importance of Type D and loneliness as independent predictors of depression was also observed in a few other studies.[15, 18, 52-55] One recent study even found that Type D personality not only independently predicted depression status over time, but also predicted the different depression trajectories. Furthermore, Type D personality and other psychological vulnerabilities were found to be especially important for persistent depression.[15] Based on the fact that Type D personality is constructed out of a negative affect scale which has a potential overlap with depression, these current findings could be, in part, expected.[56] However, Type D and depression clearly differ in the presence of social inhibition and in their conceptualization as either a disorder or a personality trait.[57] This is supported by evidence from factor analytic research which shows that items from the Type D personality scale are different from depressive symptoms.[58] Furthermore, intra-individual variability in depressive symptoms over time did not affect Type D status,[31] while Type D personality is able to predict major cardiac events above and beyond concurrent symptoms of depression.[57] In relation to loneliness, more insight is needed into the prevalence and cause of loneliness among HF patients with depression. Loneliness can develop not only as a result of inadequate social support after a negative life event, but can also be caused by alienation or a distorted view on social support of the depressed patients.[59] A focus on conserving and rebuilding adequate social relationships could therefore be of great value for the well-being and survival of these patients.

This study has a number of limitations. The three theoretical models we use in our analyses do not exist in isolation, but interact with one another via pathways that are not fully understood. Therefore, our analyses were not able to provide information on the

directionality of any relationship between inflammation, disease severity and personality. The number of personality variables used in our analyses was limited, therefore future studies ought to expand this model by also including psychological vulnerability variables such as low-reinforcement, low-self esteem and neuroticism. Furthermore, since about 60% of the patients were males with NYHA class I the results of this study cannot necessarily be extrapolated to women with HF in general or to patients with clinical heart failure, respectively. For the assessment of depression we used a self-report measure, and caution is required regarding the outcomes of the analyses in relation to a clinical diagnosis of depression. Another aspect of attention in regard to the HADS is its lack of somatic items of depression, thereby potentially making it more difficult to find a relationship with inflammation induced 'sickness behavior'. However, sickness behavior is also known to manifest itself mentally and previous studies have shown that also cognitive/affective depressive symptoms can be prospectively associated with sTNFr1 and sTNFr2, independent from clinical and demographic covariates.[60] Therefore, this should not have been a major problem in this study. A number of potential predictors of depression were not assessed in this study, including C-reactive protein, autonomic nervous system dysfunction, and platelet dysfunction.[61] Most of these variables have not been intensively studied as plausible alternative mediating pathways for depressive symptoms in HF thus far. Lifestyle and health behaviors, such as smoking, alcohol use, diet and exercise, have also been associated with depression and are a possible mediator in the depression-to-inflammation relationship.[8, 46,50] In this study only BMI was taken into account in the analyses to prevent overfitting of the regression model. Current findings indicate that BMI is significantly associated with depressive symptoms. However, since no formal tests of mediation were performed, the role of BMI as mediator remains unconfirmed.

CONCLUSION

Determining the predictors of depression in HF patients is important to identify potential targets for novel interventions. This study shows that clinical parameters [i.e. NYHA functional class, co morbidity] and personality factors [i.e. Type D personality and loneliness] have to be considered as concomitants of depressive symptoms in patients with HF. Further studies are warranted to replicate these findings, to further explore the relative importance of these models with a focus on sample characteristics, untested variables (i.e. lifestyle

factors, physiological risk markers), secondary effects and the complexity of psychological, and physiological and pharmacological pathways to be able to disentangle and resolve the 'system' of cause-effect relationships. Since we used only two measures for personality we propose future studies to explore a broader range of cognitive, behavioral, and interpersonal personal vulnerabilities, but also social and behavioral risk factors. Based on current findings it may be too premature to suggest the inclusion of personality factors in risk algorithms for depression in HF patients, however it seems information on the personality of the patient may help optimize the management and care of this subset of vulnerable HF patients in clinical practice.

Table 2: Linear regression model of depressive symptoms at baseline (n=268)[1]

	Model 1			Model 2			Model 3		
	B	SE	p	B	SE	p	B	SE	p
Inflammation	**R^2=0.061**			**R^2=0.061**			**R^2=0.061**		
TNFsr1	-1.716	1.52	.26	-2.172	1.55	.16	-2.199	1.56	.16
TNFsr2	1.123	1.85	.55	1.398	1.82	.44	1.140	1.86	.54
TNFα	.921	1.79	.61	.281	1.88	.88	.412	1.82	.82
IL-6	.589	1.03	.56	.230	1.00	.81	.246	.99	.80
IL-10	-.062	.70	.93	-.098	.71	.89	-.175	.72	.81
Disease severity	**R^2=0.121**			**R^2=0.121**			**R^2=0.121**		
NYHA class	**2.433**	.75	**.001**	**2.383**	.74	**.001**	**2.437**	.74	**.001**
LVEF	-.001	.031	.99	-.011	.03	.72	-.013	.63	.68
BNP (pmol/l)	.001	.002	.74	.001	.002	.69	.001	.002	.86
Etiology	.359	.44	.42	.218	.44	.62	.019	.49	.97
Comorbidity index	.091	.14	.51	.147	.17	.38	.190	.17	.27
Personality	**R^2=0.545**			**R^2=0.545**			**R^2=0.545**		
UCLA - loneliness	**.294**	.04	**<.001**	**.278**	.04	**<.001**	**.277**	.04	**<.001**
Type D personality	**2.598**	.55	**<.001**	**2.426**	.55	**<.001**	**2.415**	.55	**<.001**
Socio-demographic characteristics				**R^2=0.623**			**R^2=0.623**		
Age				-.005	.03	.86	-.010	.03	.76
Sex				-.488	.54	.36	-.479	.54	.37
Educational level				**1.215**	**.45**	**.007**	**1.222**	.45	**.007**
Marital status				.553	.52	.29	.478	.52	.36
BMI				**.091**	**.040**	**.02**	**.094**	.04	**.02**
Medication							**R^2=0.633**		
Aspirin							.275	.43	**.52**
Statins							-.578	.53	**.27**

[1]B, SE and p-value reported of the pooled outcomes after multiple imputation

Table 3: Linear regression model of depressive symptoms at 1-year follow-up (n=257)

	Model 1			Model 2			Model 3			Model 4		
	B	SE	p	B	SE	p	B	SE	p	B	SE	p
Inflammation	**R^2=0.045**			**R^2=0.045**			**R^2=0.045**			**R^2=0.045**		
TNFsr1	-2.731	1.71	.11	-2.794	1.72	.11	-2.636	1.73	.13	-.825	1.50	.58
TNFsr2	.968	1.95	.62	1.119	1.90	.56	1.245	1.90	.51	.803	1.51	.59
TNFα	-.104	1.78	.95	-.330	1.76	.85	-.474	1.77	.79	-1.129	1.55	.47
IL-6	.812	1.03	.43	.47	1.03	.65	.477	1.03	.64	.266	0.80	.74
IL-10	.685	.72	.34	.52	.71	.46	.584	.71	.41	.679	.56	.23
Disease severity	**R^2=0.107**			**R^2=0.107**			**R^2=0.107**			**R^2=0.107**		
NYHA class	**2.368**	.85	**.005**	**2.326**	.83	**.005**	**2.245**	.83	**.007**	**.668**	.72	.35
LVEF	-.026	.03	.45	-.036	.03	.29	-.038	.03	.27	-.030	.03	.27
BNP (pmol/l)	-.001	.002	.58	-.001	.002	.68	-.001	.002	.75	-.001	.002	.84
Etiology	.086	.46	.85	.017	.47	.97	-.213	.53	.69	-.308	.42	.47
Comorbidity index	.186	.15	.22	.339	.19	.07	.350	.19	.07	.241	.15	.12
Personality	**R^2=0.403**			**R^2=0.403**			**R^2=0.403**			**R^2=0.403**		
UCLA - loneliness	**.205**	.05	**<.001**	**.183**	.05	**<.001**	**.189**	.05	**<.001**	.018	.04	.66
Type D personality	**2.735**	.61	**<.001**	**2.578**	.60	**<.001**	**2.555**	.60	**<.001**	**1.001**	.52	**.05**
Socio-demographics				**R^2=0.421**			**R^2=0.421**			**R^2=0.421**		
Age				-.045	.03	.17	-.050	.03	.14	-.048	.03	.08
Sex				.047	.60	.94	-.008	.60	.99	.337	.50	.56
Educational level				**1.454**	.48	**.002**	**1.406**	**.48**	**.004**	.720	.39	.06
Marital status				.215	.56	.70	.264	.57	.64	-.005	.45	.99
BMI				.081	.04	.06	.084	.04	.06	.031	.04	.40
Medication							**R^2=0.432**			**R^2=0.432**		
Aspirin							.581	.46	**.20**	-.786	.37	.40
Statins							-.343	.57	**.55**	**.072**	**.49**	**.04**
Baseline depression										**R^2=0.597**		
										.615	.06	**<.001**

[1] *B, SE and p-value reported of the pooled outcomes after multiple imputation*

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CHAPTER 10

Positive affect dimensions and their association with inflammatory biomarkers in patients with chronic heart failure

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ABSTRACT

Background: In cardiac patients positive affect has found to be associated with improved clinical outcomes, with reduced inflammation being one of the potential mechanisms responsible.

Methods: Positive affect was assessed using The Global Mood Scale (GMS), Positive and Negative Affect Schedule (PANAS), and Hospital Anxiety and Depression Scale (HADS) in patient with chronic heart failure (N=210; 67±9 years, 79% men). Markers of inflammation (TNFα, sTNFr1, sTNFr2, IL-6 and CRP) were measured and averaged at three consecutive time points.

Results: The positive affect dimensions of the GMS and PANAS were significantly associated with a lower averaged levels of sTNFr2, TNFα and IL-6 ($p<0.1$), even after adjustment for clinical and lifestyle confounders. Positive affect of the HADS was significantly associated with lower averaged levels of hsCRP ($p<0.1$), but was no longer significant after correction for lifestyle confounders and depressive symptoms.

Conclusion: Positive affect is associated with reduced inflammation in patients with heart failure

INTRODUCTION

There is emerging evidence that emotions play a key role in linking psychological stress to physical health.[1,2] Apart from the detrimental effects of negative affect, such as anger, depression, and anxiety, there is a growing interest in the role of positive affect as a potentially protective factor in the progress of chronic disease.[3]

Positive affect is defined as feelings that reflect a state of high energy, full concentration and a level of pleasurable engagement with the environment, such as joy, happiness and contentment.[1] Positive affect can confer benefit to individuals beyond the feeling of well-being, given that it has been associated with an overall prolonged healthy life expectancy,[4 5] reduced blood pressure,[5-7] a higher heart rate variability[8] and a reduced risk for stroke, coronary heart disease[9] and hypertension.[3,5]

The mechanisms responsible for the link between positive affect and improved health ought to be found in behavioral and biological pathways such as a healthy lifestyle and inflammation.[2] Assuming the mechanisms between negative and positive affect are similar and acting in a opposite manners, positive affect is expected to render an anti-inflammatory effect as negative affect has been associated with higher pro-inflammatory levels.[10-12]

Indeed, previous studies have found positive affect to be associated with functional changes of the immune system,[13-16] and specifically also with lower levels of the stress hormones epinephrine, norepinephrine and cortisol.[17] These hormones are important regulators of immune functioning, and subsequently of the level of inflammatory biomarkers (i.e. Interleukin-6 (L-6), Tumor necrosis factor alpha (TNFα), C-reactive protein (CRP)) in the body.[17] IL-6 and CRP are crucial in the regulation of thrombopoiesis, the acute phase response, and the formation of fibrosis in cardiac tissue.[18] Several studies have also observed an association between positive affect and levels of Interleukin-6 (IL-6) and C-reactive protein (CRP).[2,19-22] Some studies found an inverse association between positive affect and levels of IL-6 in healthy adults,[19, 20] women[21] or men,[22] adjusting for age, ethnicity, socioeconomic status, body mass index (BMI), smoking and depressed mood.

Furthermore, positive affect was associated with reduced levels of the inflammatory marker CRP in healthy women from the Whitehall II study, but not in men.[21] There are also several studies linking mood to tumor necrosis factor alpha (TNFα) and its receptors, which also play a pivotal role in relation to HF as cells within the myocardium are able to synthesize

and release TNF-α in response to cardiac stress, such as left ventricular pressure, or volume overload. TNF-α release then leads to an increase in soluble receptors sTNFr1 and sTNFr2 which act as immunomodulatory elements.[23] However, most studies on TNFα and its receptors have used negative affect states such as depression,[24] and did not further investigate positive affect.

Despite several studies reporting an association between positive affect and lower levels of inflammation, the association is not always found for all cytokines,[20] and sometimes even entirely absent.[25] An explanation for this could be the use of different instruments for positive affect in a variety of populations, making it difficult to compare the results. Moreover, since there seems to be little agreement on what is actually meant by positive affect,[1] one can also not just assume that what these instruments measure is identical. On top of that, many studies examining the relation between positive affect and prognosis or survival are limited by a lack of control for potential confounders such as negative affect.

Therefore the aim of this study was first of all, to examine the differences in three positive affect constructs which are commonly used in cardiovascular populations, i.e. the Global Mood Scale (GMS), the Positive and Negative Affect Schedule (PANAS) and the positive affect dimension of the Hospital Anxiety and Depression Scale,[1] in a single patient population, and second, to examine whether these positive affect constructs differ in their association with five inflammatory biomarkers (e.g. TNFα, sTNF1, sTNFr2, IL-6, CRP) using a prospective mixed model, additionally correcting for depressive symptoms.

METHODS AND MATERIALS

Study population and design

Consecutive outpatients with a diagnosis of heart failure (HF) were recruited from the St. Elisabeth Hospital, Tilburg, the Netherlands between June 2006 and February 2009. Inclusion criteria were: LVEF ≤40%, stable on oral HF medication within one month prior to inclusion, New York Heart Association (NYHA) functional class I-III, no hospital admissions in the month prior to inclusion. Exclusion criteria were >80 years of age, unable to understand and read Dutch, clinical signs of acute infection, active episodes of gout or arthritis, use of anti-inflammatory medication, other life-threatening diseases, myocardial infarction 2 months prior to inclusion, and cognitive impairments or psychiatric comorbidity (except for mood disorders). Of the 270 patients that complied with the inclusion criteria, 26 patients refused

participation, died or did not return the baseline questionnaire, leaving 244 patients eligible for analyses. In total 34 patients had no cytokine measurements and were excluded from the final analyses leaving 210 (78%) HF patients. Patients were asked to complete a set of questionnaires at inclusion assessing socio-demographic and psychological variables. This questionnaire was returned in a stamped and pre-addressed envelope. If the questionnaire was not returned within two weeks, patients received a reminder telephone call or letter. All questionnaires were checked for completeness. Blood samples for cytokines measurement and clinical laboratory values were drawn at baseline, 12 months and 18 months follow-up. The blood draws were taken across the day during regular scheduled visits at the outpatient clinic. Patients were instructed not to exercise, smoke or drink coffee immediately prior to the blood draws. The study was approved by the Medical Ethics Committee of the St. Elisabeth hospital in Tilburg and conducted in accordance with the most recent version of the Helsinki Declaration (2008). All patients provided written informed consent before entering the study.

Measures

Demographic, lifestyle and clinical variables

Demographic variables comprised gender, age, marital status (having a partner vs. having no partner), and educational level (primary school vs. secondary school and above). Clinical variables included time since HF diagnosis, etiology of HF (ischemic vs. non-ischemic), previous cardiac events (i.e., previous myocardial infarction (MI), coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI)) and prescribed medications (beta-blockers, calcium antagonists, nitrates, aspirin and other platelet-aggregation inhibitors, anticoagulants, ACE-inhibitors & ARB's, statins, diuretics and psychotropic medication). Lifestyle variables included current smoking status, exercise and BMI. Disease severity variables included etiology left ventricular ejection fraction (LVEF), brain natriuretic peptide (BNP) and New York Heart Association functional class (NYHA), and medical co morbidity (i.e., included presence of COPD, peripheral arterial disease, hypertension, lipid dysfunction, gastrointestinal disease, diabetes, liver disease, and kidney failure). Kidney function was measured by calculating the glomerular filtration rate of creatinine using the MDRD formula, and kidney dysfunction was defined as a GFR_{creat}<60mL/min per 1.73m.[26,27] Lifestyle variables included current smoking status, exercise and BMI.

Positive affect

Positive affect was measured using three different measures which are widely used in the field of cardiovascular behavioral medicine; i.e., the positive affect items of the Global Mood Scale (GMS), the positive items of the Positive and Negative Affect Schedule (PANAS) and the positive affect dimension of the Hospital Anxiety and Depression Scale. The Global Mood Scale (GMS) comprises 10 negative ("fatigued" and "listless") and 10 positive ("lively" and "hard working") mood terms that especially tap vitality concepts that are commonly reported by cardiac patients.[28] The respondent is asked to rate on a 5-point Likert scale (ranging from 0, *not at all* to 4, *extremely*) the extent to which he/she has experienced each mood state lately; scores on both the NA and PA scales range from 0 to 40. Both the NA and PA scales of the GMS are internally consistent; i.e., Cronbach's α = .94 and α = .91 [28], α = .87–.94 and α = .90 and α = .90,[29] respectively. The GMS has also been shown to be responsive to treatment-related changes in negative and positive affect among cardiac patients.[29,30]

The PANAS is a 20-item self-report measure of positive and negative affect developed by Watson, Clark, and Tellegen (1988b).[31] NA and PA reflect dispositional dimensions, with high-NA epitomized by subjective distress and unpleasurable engagement, and low NA by the absence of these feelings. By contrast, PA represents the extent to which an individual experiences pleasurable engagement with the environment. Compared to the GMS, this scale is relatively more cognitive-motivational oriented with items such as "strong" and "inspired".[32] Each item is rated on a 5-point scale ranging from 1 = *very slightly or not at all* to 5 = *extremely* to indicate the extent to which the respondent has felt this way in general. Watson et al. [31] reported Cronbach's alpha coefficients for a general period, alpha was .88 for Positive Affect and .87 for Negative Affect. Test-retest correlations for an 8-week period ranged from .47 to .68 for Positive Affect, .39 to .71 for Negative Affect (for the general time period, Positive Affect stability = .68, Negative Affect stability = .71).

Previous research in myocardial infarction patients showed the HADS comprised a subscale to assess (the absence) of positive affect (e.g. anhedonia) in cardiac patients.[33] Explanatory factor analyses was used to extract the items of the positive affect dimension, i.e., being cheerful, looking forward with enjoyment to things, being still able to enjoy things and seeing funny side of things. Thus, this subscale contains the strongest hedonic valence

compared with the GMS and PANAS. Corrected item-total correlations ranging between 0.69/0.72 and Cronbach's α=0.86 indicated a high internal consistency of this four-item dimension.[33] Each item of the HADS has a 4-point response scale ranging from *0= just as much/most of the time* to *3= not at all* to indicate how the respondent has felt in the last week. Since normally higher item scores of the HADS represent a lower positive affect, we reversed the scoring of the HADS positive affect scale to make the interpretability the same as for the GMS and the PANAS positive affect scales, thus higher scores representing a higher positive affect.

Depressive symptoms

Depressive symptoms were assessed to be able to control for this widely used concept in relation to inflammation. The 10-item Center for Epidemiological Studies Depression Scale (CES-D),[34, 35] a measure that has frequently been used to measure depressive symptoms in CHF, was assessed at a baseline. The 10 items are answered on a four-point Likert scale ranging from 0 (rarely or none of the time) to 3 (most or all of the time). A cut-off score of 11 is indicative of "significant" or "mild" depressive symptomatology. Reliability statistics with the 10-item CES-D were found to be comparable to those reported for the original CES-D. The sensitivity of the 10-item CES-D was 97%; specificity, 84%; and positive predictive value, 85% .[36]

Inflammation

Levels of tumor necrosis factor (TNF)-α, soluble TNF receptors 1 and 2 (sTNFr1 & sTNFr2), interleukin (IL)-6 and high sensitive C-reactive protein (hsCRP) were obtained using standard hospital protocol. Venous blood samples were drawn and centrifuged at baseline. Blood was allowed to clot at room temperature for at least 20 minutes and centrifuged. Aliquoted serum samples were stored at -80°C in anticipation of further processing. Concentrations of IL-6 (sensitivity: 2 pg/ml) and TNFα (sensitivity: 1.7 pg/ml), were measured using a solid-phase, enzyme labeled, chemiluminescent immunometric assay (Immulite 1000, Siemens Healthcare Diagnostics Breda, The Netherlands). Soluble tumor necrosis factor receptors (sTNFR1 and sTNFR2; sensitivity for both: 15.6 pg/ml) were measured using quantitative enzyme-linked immunosorbent assay (Hycult Biotechnology, Uden, The Netherlands). hsCRP was analyzed on a Cobas C501 using a particle-enhanced immunoturbidimetric assay (Roche

Diagnostics, Almere, The Netherlands). All tests were measured in accordance with the manufacturer's recommendations. The sensitivity of all tests was calculated as the mean of six zero-values plus three SDs extrapolated on the standard curve. The intra-assay variation was less than 10%, and the inter-assay variation less than 11%.

Statistical analyses

To compare the demographic and clinical characteristics between patients with and without cytokine measurements, *t* tests, Mann-Whitney U tests, or χ^2-tests were used depending on the measure and variable distribution. The descriptives of the cytokines over time are given for the non-transformed levels of sTNFr1, sTNFr2, TNF-α, IL-6 and hsCRP, median and interquartile range. Prior to analyses, the cytokine data was tested for outliers and its distribution; due to its skewed distribution, the data were transformed using log10. We used exploratory factor analyses (i.e. principal components analysis with oblimin rotation) to examine differences in positive affect dimensions that were assessed in the current study. The scree plot was used as a criterion for the number of underlying components to extract. To examine the relation between the positive affect constructs, and the relation between the constructs and the cytokines over time, a Pearson's correlation coefficient was calculated.

For the multivariate analyses we used the linear mixed model procedure (covariance model: *unstructured*, maximum likelihood (ML) estimate) in SPSS version 17.0. The dependent cytokine variables were measured at baseline, 12 months and 18 months, and all available data was used, thereby limiting bias and preserving statistical power. The mixed multivariate analyses were composed of four models. The first model (Model 1) is the base model in which positive affect was entered together with age, gender and time. In the second model (Model 2), the first model was complemented by BNP, diabetes, kidney failure, statin and aspirin use. In the third model (Model 3), BMI, exercise, smoking and educational level were added to the first model, and in the fourth model (Model 4) depressive symptoms were added to Model 1 by using the continuous CES-D scores. The choice of covariates was based on theoretical evidence of possible confounders of inflammation.[6, 21, 37-43] Positive affect (baseline) and other covariates were entered into the model as fixed effects to examine whether they are significantly associated with the (variance of) the averaged inflammatory biomarkers over time. No post-hoc corrections were made for multiple

comparisons due to the high probability of finding small effect sizes, the moderate to high correlation between the cytokines, and the explorative nature of the analyses.

RESULTS

Patient characteristics

The mean age of the 210 patients was 66.7±8.7 year, 166 patients (79%) were men. Complete information on the demographic, clinical and psychological baseline characteristics of the patients is shown in **Table 1**.

Table 1: Socio-demographics of patients at baseline

	Total (N= 210) Mean ± SD; n (%)
Demographics	
Male	166 (79%)
Age (yrs)	66.7±8.7
Partner	161 (77%)
Education	
Primary school	71 (34%)
Secondary school and above	139 (66%)
Clinical	
Etiology	
Ischemic heart disease	138 (66%)
Other (congenital, bacterial, valvular disease e.g.)	72 (34%)
NYHA functional class	
I	116 (55%)
II	76 (36%)
III	18 (9%)
LVEF	33.70±6.73
BNP (pmol/L)	70.3±118.6
Chronic obstructive pulmonary disease	44 (21%)
Hypercholesterolemia	142 (68%)
Diabetes	61 (29%)
Kidney failure	65 (32%)
Current smoker	45 (23%)
BMI	28.1±5.3
Medication use	
Beta blockers	139 (66%)
Nitrates	106 (51%)
Angiotensin-converting enzyme inhibitors	121 (58%)

Angiotensin-receptor blockers	70 (33%)
Statins	146 (70%)
Diuretics	131 (62%)
Psychotropic medication	36 (17%)
Aspirin	75 (36%)
Postive affect (baseline)	
GMS	22.4±7.8
PANAS	32.8±7.1
HADS	9.6±2.4
Depression (baseline)	
CES-D	6.5±4.7
CES-D ≥11 (presence of depressive symptoms)	40(19%)

CES-D = Center for Epidemiological Studies Depression Scale; GMS= Global Mood Scale; HADS= Hospital Anxiety and Depression Scale; PANAS=Positive And Negative Affect Schedule

Cytokines levels

Cytokine levels were measured at baseline, 12 months and 18 months follow-up. Cytokine levels were missing at random in some patients for logistic and practical reasons. From the total number of patients in the study (n=244), patients excluded from the analyses due to missing cytokine values (baseline: n=34) did not differ systematically from patients who did have positive affect baseline scores (baseline: n=210) on clinical, demographic, and psychological characteristics, except that patients excluded from the analyses were more likely to be on betablockers (88% vs. 66%, χ^2=6.65, *p*=.010). See **Table 2** for the median and interquartile range (IQR) of the non-transformed cytokine levels at baseline, 12 months and 18 months.

Positive affect dimensions

The positive affect constructs of the GMS, PANAS and HADS had a Cronbach's α coefficient of .87, .91 and .78, respectively. Exploratory factor analysis revealed that the three positive affect constructs loaded on 3 separate components, thereby indicating that the GMS, PANAS and HADS measure different dimension **(Table 3)**. The correlation between component 1 (mainly GMS) and 2 (mainly HADS) was .12, between 1 and 3 (mainly PANAS) was .56 and between 2 and 3 was .04. GMS item 17 (Cheerful) loaded together with the positive affect construct of the HADS, however the loadings on the second component were small.

Correlation coefficients between the GMS, PANAS and HADS scales were r=.726 (p<0.001) between GMS and PANAS, r=.52 (p<0.001) between the GMS and HADS, and r=.46 (p<0.001) between PANAS and HADS. The factor analyses, correlation and reliability coefficient were calculated on the full sample size at baseline of n=244 HF patients.

Table 2: Cytokine levels at baseline, 12 and 18 months follow-up

	Baseline median (IQR)	12 months median (IQR)	18 months median (IQR)
sTNFr1 [ng/ml]	6.2 (3.1)	7.2 (3.9)	7.5 (4.5)
sTNFr2 [ng/ml]	0.99 (0.91)	0.81 (0.99)	0.96 (0.94)
TNFα [pg/ml]	11.9 (5.2)	11.9 (4.7)	11.9(4.1)
IL-6 [pg/ml]	3.9 (3.3)	3.6 (3.2)	3.4 (2.4)
hsCRP [mg/L]	2.9 (4.8)	2.5 (4.3)	2.1 (3.5)

hsCRP = high sensitive C-reactive protein; IL6 = interleukin 6; TNFα = tumor necrosis factor α; sTNFr1/2 = soluble tumor necrosis factor receptor 1 or 2
Cytokine levels are non-transformed, N = 210 max
Median and IQR = interquartile range are shown

Positive affect and cytokine levels

Correlation analysis was performed for baseline positive affect and cytokine levels over time, in which IL-6, sTNFr2 and TNF-α showed consistent negative associations with positive affect while hsCRP and sTNFr1 showed almost no associations (*data not shown*). TNFα had a significant correlation with the GMS positive affect at baseline (r=-.157, p=.036) and with the GMS and PANAS at 18 months (r=-.333, p=.004 and r=-.327, p=.004, respectively). For IL-6 the correlation was significant with the GMS and PANAS at baseline (r=-.200, p=.008; r=-.162, p=.028, respectively) and with the GMS and HADS at 18 months (r=-.232, p=.047; r=-.261, p=.024). sTNFr2 correlated negatively with positive affect at most occasions (significant correlations ranging from r=-.17 (p=.017) at baseline for the HADS to r=-.26 (p=0.002) for the GMS).

Using mixed multivariate modeling the three positive affect constructs were analyzed as predictors of the averaged level of inflammatory markers over time **(Table 4)**. The GMS positive affect score was significantly associated with sTNFr2 ($F_{(1,187)}$=9.17, p = .003), TNFα

($F_{(1,186)}$=9.19, p=.003), and IL-6 ($F_{(1,195)}$=7.72, p=.006), but not with sTNFr1 ($F_{(1,142)}$=1.26, p=.26), or hsCRP ($F_{(1,202)}$=.90, p=.34) adjusted for age, gender and time (model 1). Further adjustment for clinical confounders (model 2), lifestyle confounders (model 3) and depressive symptoms (model 4) did not attenuate these findings (sTNFr2 range ($F_{model2(1,175)}$=7.51, p=.007 to $F_{model4(1,185)}$=4.76, p = .03), TNFα range ($F_{model3(1,186)}$=7.55, p=.007 to $F_{model2(1,175)}$=5.14, p=.025)), and IL-6 range ($F_{model2(1,185)}$=4.57, p=.003 to $F_{model4(1,192)}$=7.03, p=.009). The PANAS positive affect scores was significantly associated with lower levels of sTNFr2 ($F_{(1,173)}$=8.11, p=.005) and TNFα ($F_{(1,166)}$=4.95, p=.028) after adjustment for age, gender and time, and also after additional correction for clinical and lifestyle confounders (p<.05 for all). Only the association between the PANAS positive affect and sTNFr2 remained marginal significant ($F_{(1,175)}$=3.78, p=.053) after an additional correction for depressive symptoms. The PANAS was not significantly associated with sTNFr1 or hsCRP before or after adjustment for clinical and lifestyle confounders and depressive symptoms (p>.1 for all), and only marginally significant in relation to IL-6 (p<.1 for all models).

The positive affect score of the HADS was not significantly associated with sTNR1, TNFα or IL-6 in any of the models (p>.1 for all). HADS positive affect was significantly associated with sTNFr2 and hsCRP after correction for age, gender and time (sTNFr2: $F_{(1,196)}$=5.45, p=.021; hsCRP: $F_{(1,210)}$=5.72, p=.018) and clinical confounders (sTNFr2: $F_{(1,185)}$=4.63, p=.033; hsCRP, $F_{(1,200)}$=3.61, p=.059). Only the association with sTNFr2 remained marginally significant after correcting for lifestyle confounders ($F_{(1,198)}$=3.48, p=.068), but this association was attenuated after correction for depressive symptoms ($F_{(1,189)}$=.57, p=.45). The covariates introduced in the first model of the mixed modeling included age, gender and time. Older age increased the level of sTNFr1, sTNFr2 and IL-6 in the analyses of the GMS, PANAS and HADS (all *p*s<.01), while male gender appeared to lower the cytokine levels of sTNFr1 (GMS) and sTNFr2 (PANAS and HADS). Comparing baseline cytokine levels with those at 12 and 18 months follow-up, there seems to be a consistent increase in averaged sTNFr1 and TNFα over time (GMS, PANAS and HADS), almost no difference in sTNFr2 and hsCRP levels and an decrease in levels of IL-6 (GMS, PANAS and HADS).

Table 3: Factor analysis of positive affect measures at baseline

Pattern Matrix			
Items	Component		
	1	**2**	**3**
GMS 09 - Lively	**.94**	.24	.07
GMS 05 - Bright	**.94**	.02	.29
GMS 07 - Hard working	**.94**	.02	.07
GMS 17 - Cheerful	**.94**	**.37**	.07
GMS 20 - Self-confident	**.94**	.02	.27
GMS 16 - Sociable	**.94**	.02	.07
GMS 04 - Dynamic	**.69**	.01	.14
GMS 02 - Active	**.66**	.05	.12
GMS 13 - Enterprising	**.55**	.01	.01
GMS 14 - Relaxed	**.44**	**.37**	.07
HADS 04 - Positive attitude	.01	**.81**	.02
HADS 12 - Looking forward	.02	**.79**	.02
HADS 02 - Enjoying things	.16	**.77**	.07
HADS 06 - Feeling cheerful	.11	**.75**	.06
PANAS 14 - Inspired	.15	.04	**.86**
PANAS 05 - Strong	.04	.05	**.86**
PANAS 09 - Enthusiastic	.04	.20	**.85**
PANAS 12 - Alert	.04	.11	**.76**
PANAS 16 - Determined	.21	.02	**.69**
PANAS 10 - Proud	.28	.05	**.62**
PANAS 17 - Attentive	.23	.01	**.58**
PANAS 03 - Excited	.24	.24	**.57**
PANAS 01 - Interested	.20	.01	**.55**
PANAS 19 - Active	.00	.02	**.30**

GMS=Global Mood Scale; HADS= Hospital Anxiety and Depression Scale; PANAS= Positive And Negative Affect Schedule
Pattern matrix N=244
Items sorted based on component score cut-off .30

Table 4: Mixed multivariate model of positive affect according to HADS, GMS and PANAS

	sTNFr1	sTNFr2	TNFα	IL-6	hsCRP
GMS positive affect					
Model 1	O	– – –	– – –	– – –	O
Model 2: clinical confounders	O	– – –	– –	– –	O
Model 3: lifestyle confounders	O	– –	– – –	– –	O
Model 4: depression	O	– –	– – –	– – –	O
PANAS positive affect					
Model 1	O	– – –	– –	– –	O
Model 2: clinical confounders	O	– – –	– –	–	O
Model 3: lifestyle confounders	O	– –	– –	–	O
Model 4: depression	O	–	O	O	O
HADS positive affect					
Model 1	O	– –	O	O	– –
Model 2: clinical confounders	O	– –	O	O	–
Model 3: lifestyle confounders	O	–	O	O	O
Model 4: depression	O	O	O	O	O

hsCRP = high sensitive C-reactive protein; IL6 = interleukin 6; TNFα = tumor necrosis factor α; sTNFr1/2 = soluble tumor necrosis factor receptor 1 or 2

***O** = nonsignificant p>.1; **–** = negative association p<.1; **––** = negative association p<.05; **–––** = negative association p<.01; **+** = positive association p<.1; **++** = positive association p< .05; **+++** = positive association p < .01*

Model 1: Positive affect + age + gender + time (baseline vs. 12 or 18 months follow-up)

Model 2: Model 1 + BNP, kidney failure + diabetes + aspirin use + statin use

Model 3: Model 1 + BMI + activity level + smoking + education level

Model 4: Model 1 + Depression (CES-D continuous score)

In relation to the clinical confounders, kidney failure significantly increased averaged levels of sTNFr1, sTNFr2, TNFα and IL-6 over time (GMS, PANAS and HADS). Higher levels of BNP also lead to a significant increase in averaged levels of IL-6 (GMS, PANAS and HADS) and TNFα (PANAS). The use of statins caused a strong decrease in hsCRP levels ($p<.01$) (GMS, PANAS and HADS). Model three which corrected for lifestyle confounders showed that a low amount of exercise significantly increased the averaged levels of sTNFr1 and hsCRP over time (GMS, PANAS and HADS). A higher BMI had only a significant effect on hsCRP (GMS, PANAS and HADS). The correction for depressive symptoms in model 4, indicated that higher depressive symptoms significantly increase the levels of sTNR2 (HADS) and hsCRP (GMS, PANAS and HADS) ($p<.01$)

DISCUSSION

Based on the factor analysis, in which the factors fell almost completely in line with the specific scales, it appears that the difference between the positive affect measures and the inflammatory markers could well be explained by the presence of method-variance, in which the variance is attributable to the measurement method rather than to the constructs the measures represent. However, looking at these results in combination with those from previous literature, there seem to be consistent differences in the relation between different positive affect measures and inflammation,[19,20,25] thereby suggesting the explanation is more likely to be sought elsewhere. At the same time, as this is the first study examining three different positive affect measures in the same patient sample, it is difficult to give clear-cut alternative explanations for these differences in findings.

Previous studies on the negative affect (NA) of the GMS and PANAS found that the GMS-NA was more focused on emotional exhaustion while the PANAS-NA was focused more on anxious apprehension, thereby suggesting that the GMS taps a unique form of negative mood states that is not incorporated into the PANAS.[44] Therefore, this could be the case for positive affect as well in which the GMS seems to focus more on emotional *vitality*, whereas the PANAS seems to be focused more on emotional *motivation*, which could suggests that the GMS and PANAS positive affect measures cannot necessarily be used interchangeable.[44]

Another potential explanation, analogue to studies relating positive affect and cardiovascular function, could be a difference in the *type* and *intensity* of the emotional state experienced. According to previous literature one can make a differentiation between

activated (e.g. enthusiastic, joyful) and non-activated (e.g. calm, content) positive affect,[1, 2,17] in which activated emotions are more likely to influence health. However, although this being an interesting aspect to consider in research on positive affect, there seem to be no clear cut differences between the GMS, PANAS and HADS in assessing primarily activated emotions. The fact that the HADS was not designed a priori to measure positive affect, and perhaps has a stronger cognitive component (e.g. optimism, attitude) seems therefore more likely. Yet another explanation could be the difference in *timeframe* asked for by each scale's set of instructions. One could speculate that by measuring positive affect *in general* (e.g. PANAS) in comparison to *last week* (e.g. HADS) could have led to differential associations caused by performing state vs. trait assessments of positive affect. Rather than their content and timeframe also the *clustering of questions* and *response alternates* could be responsible for the difference between the measures, however the probability of this seems low since all three measures use a 4-or 5 point Likert response scale and have mixed the negative and positive affect items.

Results from the mixed modeling confirm the findings of the factor analysis by showing that although the models of sTNFr1, sTNFr2, TNFα and IL-6 appear fairly similar in their associations with the covariates (e.g. age, time, BMI, BNP, kidney failure and statin use), the association with positive affect differs depending on the construct used. For sTNFr1, sTNFr2, TNFα and IL-6 and hsCRP the results for the positive affect scales of the GMS and PANAS are almost similar (except for the model including depression). However, the HADS positive affect scale found no significant association with TNFα or IL-6 at all, while it was the single construct that found an association with hsCRP in the first and second model.

Adjustment for depression changed the association between the PANAS and TNFα and IL-6, and also between the HADS and sTNFr1 and hsCRP. The CES-D scores for depressive symptoms were only significant with respect to hsCRP (PANAS and HADS) and sTNFr2 (HADS). This could indicate that positive affect moderates the cardiovascular response to negative affect[2] or even that positive emotions may be a better predictor of inflammatory function and clinical outcomes than negative emotions.[45-47] Positive affect may therefore represent unique components of psychobiological resilience,[48] and interventions to maintain positive affect during stressful situations could be critical in obtaining lower numbers of cardiac mortality.[49] Then again, evidence also suggested that changing trait effect may not be easy

or effective, since it is also possible that stable genetic components influence both affect and inflammation.[50]

The findings of this study are in concordance with the scarce amount of existing previous literature, which is scattered among multiple different study populations varying from health adults to rheumatoid arthritis and coronary heart disease. Previous studies, of which only few corrected for depressive symptoms in their multivariate analysis, mostly originate from Cohen, Steptoe and colleagues.[5, 13-15] In relation to our current findings the Whitehall II study is the most eminent. In this study positive affect was assessed by asking participants how happy, excited, or content they felt immediately after saliva collections using four response options *(not at all - extremely)*. They found that positive affect was associated with reduced levels of IL-6 and CRP, in healthy women.[5] In this case it seems that the differences in populations and positive affect measure did not alter the results on the association with inflammation. Other studies found that plasma and soluble IL-6 receptors are associated with psychological well-being in aging women and that positive affective style covaries with stimulated IL-6 production in a middle-aged community sample.[19, 20] These studies used the MASQ (Mood and Anxiety Symptom Questionnaire) and the PANAS to measure positive affect, respectively. Similar to our findings Prather et al. did not find any association between TNF-α and the PANAS positive affect scale. As to our knowledge there are no other previous study on the relation with positive affect and the TNF-family, except for mood induction studies with TNFα.[51]

A recent paper from Andreasson et al. found no evidence on a relation between positive affect, as measured by four items of the CES-D, and IL-6. This is interesting since the positive affect items of the HADS and CES-D are both focused on anhedonia, and appear fairly similar (HADS: *"I feel cheerful"*, CES-D: *"I felt happy"*).

Based on the mixed modeling results the most important covariates of increased cytokine levels appeared to be time, age, gender, BNP, kidney failure, statin use, BMI and exercise. Kidney dysfunction, a lower amount of physical exercise, older age, female gender, a higher BMI and increased BNP levels were associated with higher averaged cytokine levels of soluble TNFr1 and TNFr2, TNFα, IL-6 and hsCRP (depending on positive affect measure). Statin use was associated with lower averaged levels of hsCRP as found in previous literature.[52] The effect of time differed between the cytokines.

A number of limitations must be acknowledged. First, except for including gender as a covariate in our multivariate analyses we did not specifically look whether the association between positive affect and cytokine levels was different among men and women, which could have affected our results based on the gender differences observed in the Whitehall II study. Therefore future large scale studies are necessary allowing statistical analyses with stratification into different age and gender groups. Furthermore, we did not correct for multiple comparison testing in this study since it was explorative in nature. As a result our Type I error is increased and the external validity decreased, which possibly overestimates some of the effects. In this study the association of positive affect with immune functioning at baseline was even maintained at 18 months follow-up, but since this study only included information on positive affect at baseline the effect of changes in positive affect over time on the cytokine levels is unknown. Therefore the question formulated by Dockray and Steptoe whether positive affect should be sustained to lead to an overall reduction in the activation of immune systems still remains unanswered. Furthermore, although we cannot rule out the possibility of reversed causality, comorbidity and disease severity measures have been controlled for, making their influence as the primary cause of the association unlikely. The percentage of women in this study was relatively low, which could affect the generalizability of the results to women with HF in general. About 20% of the patients were lost due to missing values in cytokines. A number of potential predictors of changes in cytokine levels over time were not assessed in this study due to a possible over fit of the mixed model, including socio-economic status, exercise, smoking and various other available comorbidities, medication and clinical variables. However, in our view, the most relevant variables have been selected to be included in the models.

CONCLUSION

Although research on the psycho-neuro-immunological mechanism in which positive affect can influence health might still be in its infancy, positive affect is increasingly recognized for its beneficial effect on physical health in general, but also for specifically improving prognosis and lowering mortality rates in cardiac patients through its involvement in neuroendocrine, autonomic, immune and inflammatory pathways. Based on the current findings we can conclude that there is a substantial difference between the GMS, PANAS and HADS as positive affect constructs. Therefore caution has to be maintained in comparing the

outcomes in studies measuring different types of positive affect. Results indicate positive affect is an important independent concomitant of inflammation in this sample of patients with chronic heart failure. However, targeting positive affect as a potential way to improve clinical outcomes in HF patients seems premature, as it is important to first attain a common view on the meaning of positive affect, to replicate these findings using other social and cognitive factors that might correlate with positive affect (e.g. self-esteem, optimism and self-reported health status) and to take a closer look at the exact mechanism involved between positive affect and the immune system, for instance using structural equation modeling.

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CHAPTER 11

Association between brain natriuretic peptide, markers of inflammation and the objective and subjective response to cardiac resynchronization therapy

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ABSTRACT

Introduction: Studies suggest that cardiac resynchronization therapy (CRT) can induce a decrease in brain natriuretic peptide (BNP) and systemic inflammation, which may be associated with CRT-response. However, the evidence is inconclusive. We examined levels of BNP and inflammatory markers from pre-CRT implantation to 14 months follow-up in CRT-responders and nonresponders, defined by two response criteria.

Methods: We studied 105 heart failure patients implanted with a CRT-defibrillator (68% men; age=65.4±10.1 years). The objective CRT-response was defined as a reduction of ≥15% in left ventricular end systolic volume; subjective CRT-response was defined as an improvement of ≥10 points in patient-reported health status assessed with the Kansas City Cardiomyopathy questionnaire. Plasma BNP and markers of inflammation (CRP, IL-6, TNFα, sTNFr1 and sTNFr2) were measured at three time points.

Results: Pre-implantation concentrations of TNFα were significantly lower for subjective responders compared to nonresponders (p=.05), but there was no difference in BNP and the other inflammatory markers at baseline. Objective CRT-response was significantly associated with lower BNP levels over time (F=27.31, p<.001), and subjective CRT-response with lower TNFα levels (F=5.67, p=.019).

Conclusion: Objective and subjective response to CRT was associated with lower levels of BNP and TNFa, respectively, but not with other markers of inflammation. This indicates that response to CRT is not automatically related to a stronger overall decrease in inflammation. Large-scale studies are warranted that further examine the relation between the clinical effects of CRT on inflammatory markers, as the latter have been associated with poor prognosis in heart failure.

INTRODUCTION

Cardiac resynchronization therapy (CRT) is an established treatment for patients with severe heart failure (HF) and ventricular conduction disturbances.[1-2] The biventricular pacing induced by CRT can help restore left ventricular (LV) systolic function by correcting the electro-mechanical dyssynchrony, which improves exercise capacity and reduces rehospitalization and mortality.[3-6] CRT has also been associated with favorable changes in circulating levels of neurohormones and inflammatory cytokines in HF patients.[2, 7-12] The two most commonly examined neurohormones in relation to heart failure are B-type natriuretic peptide (BNP) and N-terminal pro B-type natriuretic peptide (NT-proBNP). Natriuretic peptides are secreted by cardiomyocytes when the heart is diseased or the load on any chamber is increased. Increased BNP levels have been shown to be strong indicators for poor prognosis, but also to be of value in guiding therapy to treat heart failure. Evidence suggest a strong link between the endocrine function of the heart and the immune system, in which cytokines upregulate BNP expression while BNP has immunomodulatory functions which can induce pro-inflammatory cytokines.[13]

Many studies have shown that CRT induces a significant decrease in BNP,[7-12] but the evidence on inflammatory markers like C-reactive protein (CRP), IL-6, TNFα, and soluble TNF receptors 1 and 2 (sTNFr1, sTNFr2) is inconclusive. The majority of studies report a decrease in IL-6[2, 10, 12, 14-15] and CRP[7, 14] 3 months to 1 year after CRT implantation, but only two studies showed a decrease in TNFα and the soluble TNF receptors.[2, 16] Tarquini et al. observed no reduction in any of the inflammatory markers after CRT implantation at 1 year follow-up.[17] In addition, most of the evidence regarding these inflammatory markers is based on studies with a small number of patients, missing pre-implantation data, a short follow-up duration, and a lack of adjustment for pertinent clinical or socio-demographic covariates in the analyses.

In addition, it is not clear whether changes in the plasma levels of BNP and inflammatory markers are associated with *response* to CRT. The CRT-response can be assessed using various objective and subjective criteria. Objective response criteria are echocardiographic parameters that detect left ventricular reverse remodeling, indicating an improvement of the pump function of the heart. A subjective response criterion is patient-reported health status which has proven to be of important prognostic value in CRT patients.[18] Depending on the response criterion, 10% to 50% of patients are labeled as CRT-

nonresponders. The few studies that examined BNP and inflammatory markers in relation to CRT-response have shown mixed results,[1, 17, 19-29] and most of these studies defined CRT-response only using echocardiographic measures. As there is only a moderate association between the objective and subjective response criteria, it is possible that clinically relevant changes in health status can occur in the absence of changes in echocardiographic parameters.[18, 30] Hence, the question is to which extent the results on inflammatory markers also relate to subjective CRT-response. No study to date has examined the association between changes in subjectively reported patient-reported health status after CRT and changes in levels of BNP or inflammatory markers, and compared these to response according to objective echocardiographic parameters. For both the objective and subjective CRT response criteria, the expectation is that responders will have a stronger decrease in BNP and cytokine levels compared to non-responders.

Hence, the aim of this study was to (1) further explore the profile of BNP and inflammatory markers from pre-CRT implantation until 14 months follow-up in CRT-responders and nonresponders, defined by echocardiography as well as patient-reported health status, and (2) to additionally explore the contribution of socio-demographic, clinical and lifestyle factors to the association between BNP or inflammatory markers and the response to CRT therapy.

METHODS

Study design and participants

The sample comprised HF patients receiving a first-time CRT implantation according to the guidelines (NYHA functional class ≥ II despite optimal pharmacological therapy, LV ejection fraction (LVEF) ≤35%, QRS≥120ms) between January 2009 and August 2011 at the University Medical Center Utrecht, the Netherlands. All patients received a CRT device with defibrillator function (CRT-D). Patients participated in the 'The influence of **PSY**chological factors on health outcomes in **HEART** failure patients treated with **C**ardiac **R**esynchronisation **T**herapy: A prospective, single-center, observational study' (PSYHEART-CRT). PSYHEART-CRT was primarily designed to examine whether psychological factors moderate the effect of the objectively assessed response to CRT implantation patient-reported outcomes in patients with HF. Patients were not eligible for inclusion when aged <18 or >85 years; having insufficient knowledge of the Dutch language; a history of psychiatric illness other than

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according to Simpson's biplane method. Echocardiographic response to CRT was defined by a ≥15% relative reduction in LVESV, indicating reverse remodeling. This cut-off of 15% was based on previously performed studies,[31-32] and has shown to be a good predictor of long-term survival after CRT implantation.[33-34]

Subjective CRT-response according to disease-specific health status

The Kansas City Cardiomyopathy Questionnaire (KCCQ) was used to assess HF-specific health status.[35] The KCCQ is a 23-item, self-report questionnaire that quantifies physical limitation, symptoms, social function, and quality of life of patients with HF. These four health status subscales can be combined into a single overall summary score. Scores are transformed into a score from 0 to 100, with higher scores representing better health status. The validity and reliability of the KCCQ have previously been established and the measure was shown to be highly sensitive to clinical change in HF patients over a 6-12 week period.[35-37] In the current study, the absolute difference between baseline and 6-month KCCQ overall summary scores was calculated and dichotomized, with an improvement of ≥10 points indicating a 'health status response'. An improvement of ≥10 points represents a moderately large difference in patient health status.[37] A previous study in CRT patients using the same cut-off showed that health status responders had a 76% lower subsequent risk of dying of any cause in the first 18 months after implantation.[38] Poor health status was defined as a KCCQ score <50 points.

BNP and inflammatory markers

Levels of BNP and CRP were obtained using a standard hospital protocol. BNP was analyzed on a DxI 800 (Beckman Coulter) using a two-step chemiluminescence (sandwich) assay (Alere, San Diego, United States of America), and CRP was analyzed using a Nefelometer (BN Prospec). Interleukin (IL)-6, tumor necrosis factor (TNF-α), and soluble TNF receptors 1 and 2 (sTNFr1 & sTNFr2) were assessed in serum. Venous blood samples were allowed to clot at room temperature for at least 20 minutes and centrifuged at 4^{o}C. Aliquots of serum were stored at -80°C until batchwise analysis of cytokine levels. Concentrations of IL-6 (sensitivity: 0.156-10 pg/ml), TNFα (sensitivity: 0.5-32 pg/ml) and soluble tumor necrosis factor receptors (sTNFR1 and sTNFR2; sensitivity for both: 7.8-500 pg/ml) were measured using a quantitative enzyme-linked immunosorbent assay (R&D Systems, Abingdon, United Kingdom). All assays were performed according to the manufacturer's recommendations.

The sensitivity of all tests was calculated as the mean of six zero-values plus three SDs extrapolated on the standard curve. The intra-assay variation was less than 10%, and the inter-assay variation was less than 10.5%. TNF-α levels were below the level of detection in 67 (22.9%) samples; IL-6 levels were below the level of detection in 4 (1.4%) samples. These values were imputed using the lower detection limit/2.[39]

Statistical analyses

To compare the demographic and clinical characteristics between CRT-responders and nonresponders, *t* tests, Mann-Whitney U tests, or χ^2-tests were used depending on the measure and variable distribution. Prior to analyses, BNP, CRP and the inflammatory markers were tested for normality, after which they were transformed using log10 to obtain normal distributions. Time-course analyses of the biomarkers of the responders and nonresponders over time were done using analysis for repeated measurements on the log transformed data. The medians and interquartile ranges or the non-transformed levels of BNP, CRP and the inflammatory markers over time are given.

For the multivariable analyses we used the linear mixed model procedure (covariance model: *unstructured*, maximum likelihood (ML) estimate) in SPSS version 17.0. Separate analyses were run for BNP, CRP, IL-6, TNFα, sTNFr1 and sTNFr2 that were measured at baseline, 2 months and 14 months. Data from all available time points was used, thereby limiting bias and preserving statistical power. BNP and markers of inflammation were examined by CRT-response and covariates in five consecutive models. The first model (Model 1) is the base model in which CRT-response was entered together with age, gender and time. In the second model (Model 2: Disease severity), the first model was complemented by markers of disease severity; NYHA functional class, etiology, LVEF and QRS. In the third model (Model 3: Medication), medication use which could have affected the inflammatory makers (ACE/ARB's, amiodarone, statins and aspirin) were added to the first model. In the fourth model (Model 4: Co-morbidity), the co-morbidities COPD, renal failure and diabetes were added, and in the fifth model (Model 5: Lifestyle) the lifestyle variables and socio-economic variables BMI, smoking en educational level were added to the model. The choice of covariates was based on theoretical evidence of possible confounders of inflammation. CRT-response (at 6 months) and other covariates were entered into the model as fixed effects to examine whether they were significantly associated with the

(variance of) the averaged level of BNP and inflammatory markers over time. Furthermore, in a secondary analysis the interaction term time*CRT-response was also entered into the model. The interaction term was constructed to examine whether the level of inflammatory markers differed over time between CRT-responders and CRT-nonresponders. The results of this analysis is merely outlined in the results and not included in Table 3.

The results of multivariable analysis of the association between BNP, inflammatory markers and CRT-response are indicated by symbols ranging from p<.10 (weak association), to p<.05 (significant association) and p<.01 (strongly significant association).

No post-hoc corrections were made for multiple comparisons due to the high probability of finding small effect sizes, the moderate to high correlation between the inflammatory markers, and the explorative nature of the analyses.

RESULTS

Patient characteristics

Of 105 patients included in the PSYHEART-CRT study blood was drawn at baseline, 2 months and 14 months follow-up. The mean age of the study sample was 65.4±10.1 years and 71 (68%) patients were male. The underlying HF etiology was ischemic in 51 (48.6%) patients and 84 (80.0%) patients were in NYHA functional class III/IV (with only 2 patients being in NYHA functional class IV). The pre-implantation electrocardiogram showed a sinus rhythm in 81 (77.6%) patients and a LBBB in 58 patients (55.0%), the mean QRS duration was 160.7±25.5ms. Medication included ACE-inhibitors/angiotensin receptor blocker (92.4%), betablockers (78.1%), diuretics (87.6 %) and statins (59.0%). The patient sample had severely depressed LV function with a mean LVEF of 24.5±8.2%, mean LVESV of 171.0±68.6 mL and mean LVEDV of 225.4±75.9 mL. A transvenous LV lead placement via the coronary sinus was successfully performed in all but one patient. In this patient, who was a subjective and objective CRT-responder, an epicardial LV lead placement via video assisted thoracoscopy was required. In the majority of patients the LV lead position was posterolateral (85%). During the 14 months follow-up, 14 (13.3%) of the patients had a major adverse cardiac event including hospitalization for HF, implantation of a left ventricular assist device, CRT-explantation or death. This percentage is in accordance with randomized controlled trials on the effect of CRT-D on prognosis.[40-41] The mean baseline KCCQ score was 56.2±22.9, with 37 (35.2%) patients reporting poor health status (KCCQ score <50 points) prior to implantation.

Complete information on the demographic and clinical characteristics of the patients, stratified by CRT (LVESV and KCCQ) response, is shown in **Table 1**.

Based on a relative reduction in LVESV of ≥15% from baseline to 6 months follow-up, 47 patients were labeled as objective CRT-responder and 42 as CRT-nonresponder. Information on the LVESV change was missing for 17 patients, and these patients were not included in the analyses regarding objective CRT-response. Objective responders and nonresponders did not differ on demographic and clinical variables (p≥.05, **Table 1**). Based on an improvement of ≥10 points on the KCCQ, 58 patients were labeled as subjective CRT-responder and 47 as CRT-nonresponder. Subjective responders and nonresponders did not differ on demographic and clinical variables, except for a difference in pre-implantation QRS duration (165.7±25.4 in responders vs. 154.3±24.4 in nonresponders, p=.03 respectively, **Table 1**). Of note, there was a large discrepancy between objective and subjective CRT-response, with half of the patients showing discordant responses (kappa=-.021, p=.83).

CRT-response and inflammatory markers

Baseline concentrations of BNP and inflammatory markers did not differ between the *objective* CRT-responders and nonresponders (p>.05,**Table 2a**). BNP levels decreased significantly from baseline to 2 months and from baseline to 14 months for the objective responders (p<.001), while there was only a marginal decrease in BNP levels from baseline to 2 months (p=.05) and no difference from baseline to 14 months (p>.05) follow-up for the nonresponders. Both objective CRT-responders and nonresponders showed a significant decrease in TNFα levels from baseline to 14 months follow-up (p<.001). The levels of CRP, IL-6, TNFr1 and TNFr2 did not change significantly over time in both groups **(Table 2a)**.

The *subjective* CRT-responders had significantly lower baseline TNFα levels compared to nonresponders (p=.05, **Table 2b**). In addition, subjective responders showed a significant decrease in BNP (p<.001), TNFα (p<.001) and sTNFr1 (p=.05) levels from baseline to 14 months follow-up. In the subjective nonresponders, there was a (marginal) significant decrease in BNP and TNFα levels over time (p=.06 and p<.001, respectively), but an increase in IL-6, sTNFR1 and sTNFr2 levels (p=.03, p=.04 and p=.06, respectively) **(Table 2b)**.

Table 1: Socio-demographic characteristics of responders and nonresponders (N_{max}=105)

	Responders (N=47) ESV change≥15%	Nonresponders (N=42) ESV change <15%	P-value	Responders (N=58) KCCQ change ≥10	Nonresponders (N=47) KCCQ change <10	P-value
Demographics						
Age (years)	65.4±10.6	64.6±10.4	.73	66.0±9.1	64.7±11.3	.51
Gender (males)	29 (62)	31 (74)	.26	35 (60)	36 (77)	.09
Having a partner	36 (78)	35 (83)	.60	47 (81)	37 (78)	.81
Lower education[†]	5 (11)	6 (14)	.75	8 (12)	7 (15)	.78
Currently employed	12 (26)	9 (21)	.63	9 (16)	16 (35)	.06
Clinical factors						
Body Mass Index (BMI)	26.3±5.4	28.1±5.7	.16	27.4±5.7	27.9±6.5	.71
Ischemic etiology	18 (38)	25 (60)	.06	26 (45)	23 (53)	.44
NYHA class III/IV	35 (70)	36 (86)	.15	49 (84)	35 (76)	.22
Primary indication	41 (87)	37 (88)	.99	51 (88)	39 (83)	.58
Sinus rhythm	36 (77)	34 (83)	.60	41 (75)	35 (81)	.47
LBBB	26 (62)	22 (54)	.72	32 (58)	22 (51)	.70
Posterolateral lead position	50 (86)	43 (88)	.81	45 (92)	38 (83)	.15
QRS duration (ms)	160.5±26.2	159.2±26.0	.81	165.7±25.4	154.3±24.4	**.03**
LVEF (%)	24.3±7.1	24.9±9.6	.76	24.6±8.5	24.3±7.8	.84
LVESV (ml)	162.8±64.0	182.5±77.1	.19	175.2±70.2	165.6±67.9	.50

LVEDV (ml)	182.5±77.1	238.0±82.1	.12	231.4±71.7	215.5±72.3	.30
Upgrade from PM	4 (9)	5 (12)	.73	10 (17)	2 (4)	.11
Upgrade from ICD	5 (11)	6(14)	.81	6 (10)	7 (15)	.55
GFR (ml/minute/1.73m^2)	63.30±19.7	57.0±17.5	.12	58.8±16.9	60.4±19.6	.64
Smoking	9 (22)	5 (13)	.47	12 (24)	4 (9)	.13
COPD	10 (22)	5 (12)	.27	9 (16)	9 (19)	.80
Diabetes	7 (15)	11 (26)	.20	15 (26)	7 (15)	.23
Medication						
B-blockers	45 (78)	34 (72)	.65	39 (83)	29 (69)	.14
ACE/ARB	42 (72)	32 (68)	.67	34 (72)	30 (70)	.99
Aspirin	17 (29)	15 (32)	.83	15 (32)	13 (31)	.99
Statins	22 (47)	29 (69)	.05	34 (59)	28 (60)	.99

Results are presented as n(%), unless otherwise stated.

Significant results are indicated in bold.

** Echocardiographic response is defined as a reduction in left ventricular end systolic volume of ≥15% and health status response is defined as an improvement of ≥10 points on the Kansas City Cardiomyopathy Questionnaire at 6 month follow-up.*

† Primary school or lower

ACE/ARB= angiotensin converting-enzyme inhibitor, angiotensin receptor blocker; COPD=chronic obstructive pulmonary disease; ICD=implantable cardioverter defibrillator; GFR: glomular filtration rate; KCCQ=Kansas City Cardiomyopathy Questionnaire; LBBB=left bundle branch block; NYHA=New York Heart Association; LVEDV=left ventricular end diastolic volume; LVEF=left ventricular ejection fraction; LVESV=left ventricular end systolic volume; PM= pacemaker

Using mixed multivariable modeling, the averaged level of BNP and inflammatory markers over time was examined for CRT-responders versus nonresponders **(Table 3)**. Being an *objective* CRT-responder was significantly associated with significantly lower BNP levels over time after correction for age, sex and time (F=27.31, p<.001), but also after adjustment for disease severity (F=18.15, p<.001), medication (F=20.68, p=<.001), co-morbidity (F=19.20, p<.001) and lifestyle and socio-economic variables (F=7.30, p=.009). Objective CRT-response was not significantly associated with the overall levels of CRP, IL-6, TNFα, sTNFR1 or sTNFR2 after adjustment for age, sex and time (all ps>.05). Adjustment for disease severity, medication, co-morbidity and lifestyle confounders did not alter these findings.

KCCQ *subjective* CRT-response showed a significant association with lower levels of TNFα over time after correction for age, gender and time (F=5.67, p=.019) **(Table 3)**. These findings remained after adjustment for disease severity (F=4.54, p=.036), medication (F=5.20, p=.021), co-morbidity (F=7.56, p=.007) and lifestyle variables (F=6.28, p=.014). As in 22.9% of the cases TNFα levels were below the detection limit and substituted by the lower detection limit divided by 2, we performed a sensitivity analysis in which these cases were excluded to see if this would change our results. The association between the subjective CRT-response and TNFα remained significant for all the models after the exclusion of patients having TNFα below the detection limit. There was no association between subjective CRT-response and BNP, CRP, IL-6, sTNFr1 and sTNFr2, except for a marginal significant higher level of BNP after correction for lifestyle covariates (F=3.01, p=.086) for responders compared to nonresponders.

In secondary analyses, the interaction term time*CRT-response was added to the model, to see whether changes in BNP and inflammatory markers over time differed between responders and nonresponders. There was only a significant interaction effect for BNP, sTNFr1 and sTNFr2 levels over time in relation to subjective CRT-response (F_{BNP}=3.59, p=.03; F_{sTNFr1}=3.43, p=.04; F_{sTNFr2}=3.80, p=.03), whereby the level of BNP, sTNR1 and sTNFr2 slightly decreased for responders and increased for nonresponders leading to an intersection between 2 and 14 months follow-up *(results not shown)*. The significant main effect between BNP levels over time and objective responders and nonresponders did not change after adding the interaction effect, nor did the significant main effect change between TNFα levels and subjective responders and nonresponders.

Table 2a: BNP and inflammatory markers in responders and nonresponders over time (LVESV)

	Responders LVESV change ≥15% (N_{range}=42-47)		(N_{range}=41-44)	Nonresponders LVESV change <15% (N_{range}=38-42)		(N_{range}=36-42)	P-value
	Baseline	**2 months**	**14 months**	**Baseline**	**2 months**	**14 months**	
BNP (pmol/L)	65.0 (29.0-152.5)	40.5 (14.8-115.8)**	33.0 (9.0-72.0)**	87.5 (54.5-244.0)	74.0 (48.3-193.8)*	83.0 (44.8-166.0)	.09
CRP (mg/L)	2.0 (2.0-5.0)	4.0 (2.0-7.0)	2.0 (2.0-5.0)	3.5 (2.0-8.3)	3.5 (2.0-7.0)	2.0 (2.0-8.0)	.12
IL-6 (pg/ml)	1.21 (0.91-2.16)	1.96 (0.92-2.86)	1.56 (0.93-2.25)	2.10 (0.97-3.71)	1.76 (1.27-3.09)	1.58 (1.31-2.56)	.22
TNFα (pg/ml)	1.45 (0.89-1.98)	1.16 (0.33-1.92)	0.25 (0.25-1.31)**	1.53 (1.15-2.01)	1.41 (0.96-2.21)	0.63 (0.25-1.41)**	.76
sTNFr1 (pg/ml)	1200 (994-1460)	1190 (858-1595)	1016 (772-1700)	1335 (991-2257)	1425 (1089-1895)	1140 (912-2170)	.70
sTNFr2 (pg/ml)	2450 (1980-3480)	2560 (1855-2992)	2360 (2000-3450)	2460 (2047-3917)	2720 (1912-4052)	2560 (1945-4320)	.08

*Data are shown as medians (interquartile range); *p<.05, **p<.01 vs. the respective baseline results. In the right colomn baseline concentrations of responders and nonresponders are compared.*

N_{range}= number of observations in the analyses between baseline and 2 months, and between baseline and 14 months follow-up.

Reference range normal values: CRP= 0-10mg/l; BNP= 0-30 pmol/l.

Table 2b: BNP and inflammatory markers in responders and nonresponders over time (KCCQ)

	Responders KCCQ change ≥10			Nonresponders KCCQ change <10			p-value
	(N_{range}=54-58)	(N_{range}=51-55)		(N_{range}=43-47)	(N_{range}=37-40)		
	Baseline	**2 months**	**14 months**	**Baseline**	**2 months**	**14 months**	
BNP (pmol/L)	89.0 (32.3-293.8)	61.0 (28.5-197.5)**	57.5 (13.3-131.3)**	73.0 (42.0-113.0)	61.0 (25.5-122.3)*	48.5 (24.8-97.0)*	.16
CRP (mg/L)	3.0 (2.0-6.0)	4.0 (2.0-7.0)	2.0 (2.0-5.8)	3.0 (2.0-9.0)	3.5 (2.0-8.8)	3.0 (2.0-10.3)	.55
IL-6 (pg/ml)	1.68 (0.93-3.69)	2.07 (1.29-2.97)	1.60 (1.01-2.48)	1.51(1.93-2.42)	1.81 (0.94-3.11)	1.63 (1.09-2.68)**	.21
TNFα (pg/ml)	1.37 (0.88-1.73)	1.22 (0.63-1.88)	0.25 (0.25-1.14)**	1.58 (1.06-2.14)	1.53 (0.96-2.54)	0.85 (0.25-1.69)**	**.05**
sTNFr1 (pg/ml)	1260 (1017-1852)	1330 (1015-1772)	1040 (777-1792)*	1170 (812-1740)	1225 (875-1815)	1270 (904-1950)*	.47
sTNFr2 (pg/ml)	2620 (2047-3405)	2655 (2062-3717)	2370 (1967-3220)	2310 (1900-3620)	2755 (1747-3597)	2940 (1770-4080)**	.08

*Data are shown as medians (interquartile range); *p<.05, **p<.01 vs. the respective baseline results. In the right column baseline concentrations of responders and nonresponders are compared.*

N_{range}= number of observations in the analyses between baseline and 2 months, and between baseline and 14 months follow-up.

Reference range normal values: CRP= 0-10mg/l; BNP= 0-30 pmol/l.

Table 3: Mixed modeling of cytokine profiles over time (baseline - 14 months) in relation to CRT-response

CRT-response		BNP	CRP	IL-6	TNFα	sTNFr1	sTNFr2
$N_{range\ model\ 1\ –\ model\ 5}$		**96-105**	**85-105**	**82-105**	**81-105**	**80-105**	**80-105**
Model 1	**Responder LVESV**	**---**	**O**	**O**	**O**	**O**	**O**
Model 2: disease severity	Responder LVESV	---	O	O	O	O	O
Model 3: medication	Responder LVESV	---	O	O	O	O	O
Model 4: co-morbidity	Responder LVESV	---	O	O	O	O	O
Model 5: lifestyle confounders	Responder LVESV	O	O	O	O	O	O
$N_{range\ model\ 1\ –\ model\ 5}$		**91-105**	**88-105**	**84-105**	**89-105**	**88-105**	**88-105**
Model 1	**Responder KCCQ**	**O**	**O**	**O**	**--**	**O**	**O**
Model 2: disease severity	Responder KCCQ	O	O	O	--	O	O
Model 3: medication	Responder KCCQ	O	O	O	--	O	O
Model 4: co-comorbidity	Responder KCCQ	O	O	O	---	O	O
Model 5: lifestyle confounders	Responder KCCQ	+	O	O	--	O	O

O= no association, p >.10; − = negative association, p <.10; −− = negative association, p <.05; −−− = negative association, p<.01
+ = positive association, p <.10; ++ = positive association, p < .05; +++ = positive association. P < .01
Model 1: time, age, sex, CRT-response
Model 2 (disease severity): model 1 + LVEF, NYHA, etiology, QRS
Model 3 (medication): model 1 + ACE-inhibitors and/or angiotensin 2-antagonists, amiodarone, statins, aspirin
Model 4 (co-morbidity): model 1 + COPD, diabetes, renal failure (GFR)
Model 5 (lifestyle): model 1 + BMI, smoking, educational level

The contribution of socio-demographic, clinical and lifestyle factors to the association between BNP or inflammatory markers and the response to CRT therapy is shown in **Supplementary Tables 1a and b**. The covariates in the first model included objective/subjective CRT-response, age, gender and time. Older age was significantly associated with higher BNP, IL-6, sTNR1 and sTNFr2 levels ($p<.05$). In relation to the potential clinical confounders, patients with NYHA class III/IV showed significantly higher levels of BNP, CRP, IL-6, TNFα and sTNFr1 over time ($p<.10$). A lower LVEF and ischemic etiology were associated with a higher level of BNP ($p<.05$), while a shorter QRS duration at baseline was associated with higher CRP and TNFα levels ($p<.10$). The levels of sTNFr2 were significantly higher for CRT patients who used ACE/ARBs ($p<.05$), but lower for patients using aspirin ($p<.05$). The model adding co-morbidity showed that patients with co-morbid COPD had significantly higher levels of IL-6 and TNFα ($p<.05$). Patients with diabetes had higher levels of sTNFr1 and 2, whereas renal failure was significantly associated with higher levels of all inflammatory markers (all $ps<.10$). The lifestyle confounders BMI and smoking were associated with higher levels of IL-6 ($p<.05$), and a higher educational level was associated with an overall reduction in inflammatory markers over time (all $ps<.10$).

DISCUSSION

The aim of this study was to investigate the levels of BNP and markers of inflammation in relation to CRT-response, defined by a significant improvement on an echocardiographic (objective) or a patient-reported health status (subjective) indicator. Several hypotheses could explain the relation between inflammatory markers and the response to CRT. An increase on the load of the heart chambers, myocardial injury and underperfusion of peripheral tissues is found to increase the secretion of cytokines from mononuclear cells and the myocardium. As CRT helps to reduce the load on the heart failure chambers and restore left ventricular systolic function by correcting the electro-mechanical dyssynchrony, this could result in a decrease in BNP and pro-inflammatory cytokine levels.[5]

In the current sample, 53% of the patients were objective CRT-responders and 55% were subjective CRT-responders, which is in line with previous studies using various response criteria.[18] Multivariable mixed modeling showed that objective CRT-responders had significantly lower overall levels of BNP over time compared to LVESV nonresponders after correction for socio-demographic and clinical variables, medication and co-morbidity.

The relation was attenuated after correction for lifestyle and socio-economic variables. No differences were found between objective CRT-responders versus nonresponders in CRP, IL6, TNFα, sTNFr1 and sTNFr1 levels over time. Subjective CRT-responders showed significantly lower levels of TNFα over time compared to nonresponders, also after adjusting for socio-demographic and clinical variables, medication, co-morbidity, and lifestyle variables. The average levels of BNP and the other inflammatory markers did not differ over time between subjective CRT- responders and nonresponders. However, there was a significant interaction effect for BNP, sTNFr1 and sTNFr2 levels over time in relation to subjective CRT-response, with levels slightly decreasing for responders and increasing for nonresponders.

There are several studies describing levels of BNP and inflammatory markers after CRT implantation, but only few of these studies examined the association with CRT-response and most focused only on BNP.[9,19,21-24,29,42] Studies which did differentiate between CRT-responders and nonresponders reported mixed results, and examined (objective) echocardiographic CRT-response only. Most of these studies reported that the reduction in BNP was significantly larger or limited to responders over time,[9,19,21-24,27-28] whereas two studies reported no difference in the reduction in BNP over time after CRT implantation between responders and nonresponders.[25,29]

Only Osmancik et al. examined the association between CRT-response, based on a combination of echocardiographic and clinical criteria, and TNFα levels. Results showed no significant differences between responders and nonresponders on baseline TNFα and a significant decrease in TNFα levels in responders only.[26] In our study, we showed an overall lower level of TNFα in subjective CRT-responders versus nonresponders during the 14-month follow-up period. Besides BNP and TNFα, the current study found no evidence for an association between CRT-response and CRP, IL-6, sTNFr1 and sTNFr2 levels over time. These findings for CRP were similar to those found by Pryzbyla et al.,[15] but in contrast to two other studies that did find a significant reduction in CRP for CRT-responders only.[27-28] Likewise, only two out of the five studies on IL-6[2, 10,15,26-27] found a significant reduction in IL-6 levels after CRT implantation in CRT-responders only.[26-27] Interestingly, the levels of IL-6 in the current sample were considerably lower compared to the other studies, indicating possible differences in patient characteristics (i.e., higher age, higher percentage NYHA III-IV in other study samples) which could explain the differences in results.

The findings on the association between BNP and inflammatory markers and the socio-demographic, disease severity, medication, co-morbidity and lifestyle covariates were consistent with literature. Age, NYHA functional class, COPD, renal failure, diabetes, BMI, low educational level and smoking, were associated with higher levels of BNP or inflammatory markers, while aspirin use was associated with lower averaged inflammatory markers. The interaction effect of time by CRT-response differed between the inflammatory markers.

Overall, there was a large discrepancy in the association between BNP, TNFα and CRT-response based on the type of response measurement (objective vs. subjective). This could be explained by the poor agreement between CRT-response indicators,[18] as was confirmed in the current study with half of the patients showing discordant responses.

A number of limitations of this study should be acknowledged. First, although the present study included a larger group of patients compared to the majority of previous research in relation to this topic, the sample size of the current study was relatively small. Therefore, we had to combine patients with stable and deteriorated LVESV or health status as nonresponders. Large scale studies are needed to confirm our results. Furthermore, there are many confounders that could exert some effects in a complex field such as heart failure that could not all be taken into account in this observational study. Information on the presence of an acute infection at follow-up was missing, yet such infections could have influenced the values of the inflammatory markers. The percentage of women in this study was relatively low, which affects the generalizability of the results to women with HF. About 20% of the study patients were not included in the analyses due to missed follow-up visits or missing values in the inflammatory markers, but they did not differ systematically on baseline characteristics nor CRT-response versus nonresponse.

CONCLUSION

Objective echocardiographic CRT -response was associated with lower BNP levels in the first 14 months after implantation, while subjective patient-reported health status CRT-response was associated with lower TNFα over time. However, the differences were small and there were no associations between CRT-response and other inflammatory markers. Hence, based on our and previous results, it does not seem feasible to formulate any conclusions regarding the level of inflammatory markers as an indication of response in CRT patients.

Large-scale studies are warranted to confirm our results and to further examine whether inflammatory markers have a role to play as an indicator of CRT-response.

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Supplementary Table 1a; mixed multivariable modeling - significant covariates
LVES response

LVESV response		BNP	CRP	IL-6	TNFα	sTNFr1	sTNFr2
Model 1	Older age	+++	O	++	O	+++	+++
	Male gender	O	O	O	O	O	O
	Time 2 vs. time 1	--	O	O	O	O	O
	Time 3 vs. time 1	---	O	O	---	O	O
Model 2	NYHA class III/IV	+++	O	+	O	O	O
	EF	--	O	O	O	O	O
	Ischemic etiology	++	O	O	O	O	O
	QRS	O	--	O	-	O	O
Model 3	ACE/ARB	O	O	O	O	O	++
	Amiodarone	O	O	O	O	O	O
	Statins	-	O	O	O	O	O
	Aspirin	O	O	O	O	O	O
Model 4	COPD	O	O	+	+++	O	O
	Renal failure	O	O	O	+	+++	+++
	Diabetes	O	O	O	O	+++	+
Model 5	BMI	-	O	+++	O	O	O
	Smoking	O	O	+++	O	++	O
	Educational level	--	--	O	O	--	---

O= no association, p >.10

− = negative association, p <.10; −− = negative association, p <.05; −−− = negative association, p<.01
+ = positive association, p <.10; ++ = positive association, p < .05; +++ = positive association. P < .01
ACE=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; COPD= chronic obstructive pulmonary disease; BMI= body mass index

Supplementary table 1b; mixed multivariate modeling - KCCQ response

KCCQ response		BNP	CRP	IL-6	TNFα	sTNFr1	sTNFr2
Model 1	Older age	+++	O	++	O	+++	+++
	Male gender	O	O	O	O	O	O
	Time 2 vs. time 1	---	O	O	O	O	O
	Time 3 vs. time 1	---	O	O	---	O	O
Model 2	NYHA III/IV	+++	+	+++	+	++	O
	EF	--	O	O	O	O	O
	Ischemic etiology	+++	O	O	O	O	O
	QRS	O	--	O	O	O	O
Model 3	ACE/ARB	O	O	O	O	O	++
	Amiodarone	O	O	+	O	O	O
	Statins	--	O	O	O	O	O
	Aspirin	O	O	-	O	-	--
Model 4	COPD	O	O	+	++	O	O
	Renal failure	+	++	+	+++	+++	+++
	Diabetes	O	O	O	O	+++	+
Model 5	BMI	O	O	+++	O	O	O
	Smoking	O	-	++	O	O	O
	Educational level	--	-	O	--	---	---

O= no association, p >.10

– = negative association, p <.10; –– = negative association, p <.05; ––– = negative association, p<.01

+ = positive association, p <.10; ++ = positive association, p < .05; +++ = positive association. P < .01

ACE=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; COPD= chronic obstructive pulmonary disease; BMI= body mass index




CHAPTER 12

Summary and General Discussion

SUMMARY OF THE RESULTS

Several treatment options are available for patients with heart failure in order to improve their physical functioning and increase survival. These include the implantable cardioverter defibrillator (ICD), the biventricular pacemaker (CRT), the ICD combined with CRT (CRT-D), and the left ventricular assist device (LVAD), which are state-of-the-art cardiovascular implantable electronic devices. This dissertation focused on the influence of these innovative technologies on survival and patient well-being. Findings from studies on several heart failure samples from the Netherlands and Denmark were presented. In the current chapter, these findings are summarized, discussed and their implications for clinical practice and future research are outlined.

Health status and psychological distress in patients with heart failure

The first aim of this dissertation was to examine the health status and level of psychological distress in patients who are genetically predisposed to heart failure or implanted with an LVAD due to end-stage heart failure. Before conducting the study on LVAD patients, current knowledge on health status and psychological distress in LVAD patients was summarized in a systematic review, as presented in **Chapter 2**. The results from this review indicate that LVAD patients experience an improvement in health status over time, independent of device type and setting. However, while their physical disability becomes less prominent post implantation, many patients experience difficulties with psychological adjustment. Extensive information on patient-reported outcomes in LVAD patients is limited, with many of the existing studies having methodological shortcomings. Therefore, in order to advance the field of LVAD research and to optimize the care of LVAD patients, more well designed large-scale studies are needed to further elucidate the impact of LVAD therapy on patient-reported outcomes.

Chapters 3 and 4 reported on the results of a prospective multi-center LVAD study that examined the impact of LVAD implantation on Dutch and Canadian heart failure patients and their partners. The findings of the study indicate that the majority of LVAD patients experience a clinically relevant improvement in health status between LVAD implantation and 12 months follow-up. However, there were large differences in individual health status score trajectories, which are only partially explained by measures of disease severity pre-LVAD, co-morbidities and psychological distress. **Chapter 4** showed that LVAD

patients and their partners experienced significant levels of psychological distress after LVAD implantation which slowly abated over time. Partners of LVAD patients may fare worse than LVAD patients with respect to psychological distress. At baseline, partners were more likely to be anxious than patients, and there was a trend towards a higher prevalence of depression in partners.

Chapter 5 examined the differential burden related to having a genetic condition versus experiencing cardiac symptoms in patients with non-compaction cardiomyopathy. The health status and psychological distress of patients with non-compaction cardiomyopathy was compared with age- and gender-matched controls with acquired dilated cardiomyopathy and familial hypercholesterolemia. The results showed that cardiac symptoms are mainly responsible for the observed poor health status and elevated anxiety and depression in patients with non-compaction cardiomyopathy rather than the genetic nature of the disease. This was also found in previous studies on patients with long QT syndrome and hypertrophic cardiomyopathy,[1-3] and indicates that the majority of patients with a genetic cardiovascular condition are able to cope with their diagnosis and may not need additional psychological care support compared to patients with a non-genetic cardiovascular condition.

Psychological distress and clinical outcomes of heart failure

Current evidence suggests that psychological distress in heart failure patients may influence the progression of disease and patients' survival. The second aim of this dissertation was to examine the existing literature on the relation between psychological distress and adverse clinical outcomes, and to elaborate on possible mechanisms which could be responsible for this association. **Chapter 6** reports on the results of the use of anti-depressants and its relation with mortality in a large sample of heart failure patients extracted from the Danish National Patient Registry. Results of this study showed that use of anti-depressants after hospital discharge was significantly associated with a higher all-cause mortality risk, irrespective of a diagnosis of clinical depression and also after correction for socio-demographic and clinical risk factors. In **Chapter 7** evidence was found for a relation between psychological distress and an increased risk of ventricular tachyarrhythmia's and mortality in patients implanted with an ICD, independent of traditional risk factors. However, it is still unclear whether psychological factors constitute risk factors in their own right, or

whether they exert indirect effects via various physiological and behavioral pathways such as a decrease in heart rate variability, inflammation, HPA axis dysfunction, low physical inactivity, smoking and poor medication adherence.

Health status and psychological distress - the link with inflammation and cardiac hormones

The third aim of this dissertation was to examine the role of cardiac hormones and inflammation as potential mechanisms between psychological distress and heart failure prognosis. In **Chapter 8** no relationship was found between psychological distress (i.e. anxiety, depression and Type D personality) and NT-proBNP levels in a sample of systolic heart failure patients using a prospective study design. These results suggest that psychological distress is not confounded by disease severity markers and is therefore an independent risk marker for heart failure prognosis. Other evidence from the literature on the relation between psychological distress and BNP/NT-proBNP is mixed which could be due to large differences in the sample size across studies, the severity of distress and the large intra-individual differences in levels of BNP and NT-proBNP.

Chapter 9 reported on the results of a study that examined the relative importance of inflammation, disease severity and psychological vulnerability as the underlying etiological factors of depression in heart failure patients. Personality factors (i.e. Type D personality and loneliness) predicted depressive symptoms beyond inflammation and disease severity markers, even after correcting for potential socio-demographic confounders. Hence, it seems that inflammation is not the underlying cause of depressive symptoms or perhaps only in a small subset of patients suffering from a heightened systemic inflammatory state. These results suggest the need for more research on the differences in etiology of depression in heart failure patients and the exploration of a broader range of psychological and lifestyle variables.

Apart from the detrimental effects of psychological distress, **Chapter 10** focused on positive affect, which is increasingly recognized for its beneficial effect on prognosis in cardiac patients through its involvement in neuroendocrine, autonomic, immune and inflammatory pathways. The results suggest that positive affect is associated with reduced inflammation in patients with heart failure, also after correction for socio-demographic, clinical and lifestyle confounders and depressive symptoms. However, the relation between

positive affect and inflammation did depend on the type of positive affect measure that was used.

Chapter 11 examined the relation between inflammation and the objective and subjective response to CRT implantation, as measured by echocardiography and health status, respectively. Results showed that the objective echocardiographic CRT-response was only associated with lower BNP levels, while subjective patient-reported health status CRT-response was associated with lower TNFα in the first 14 months after implantation. This indicates that response to CRT is not automatically related to an overall decrease in inflammation, and the role of inflammatory markers as an indicator of CRT-response therefore remains uncertain.

METHODOLOGICAL AND CLINICAL CONSIDERATIONS

Study design

Except for the two systematic reviews **(Chapter 2 and 7)**, all studies included in this dissertation were based on cross-sectional **(Chapter 4)**, longitudinal **(Chapter 6)** or prospective observational data **(Chapter 3, 4, 8, 10 and 11)**. An important limitation inextricably linked to observational research is the limited potential for drawing causal inferences. Although prospective studies may give more insight into certain relations over time, they still do not provide conclusive results on causality. However, as research on the psychological impact of genetically predisposed heart failure and LVAD therapy is still in its infancy, it is appropriate first to further elucidate this topic using data from observational studies. The prospective studies with long-term follow-ups (i.e. 12-14 months) reported on in this dissertation provide the possibility to examine changes in clinical and psychological factors over time. The findings of these studies may set the stage for future research in the field of heart failure, and also point to important targets for intervention and the optimization of the quality of patient care in clinical practice.

Heart failure samples

This dissertation reports on different samples of heart failure patients which differ in terms of site of recruitment, type of treatment (i.e. CRT-D vs. LVAD), underlying etiology, disease severity and age. Due to the low prevalence of non-compaction cardiomyopathy, the low number of LVAD implantations in the Netherlands and the functional limitations and

complications in LVAD patients, the sample sizes reported on in **Chapters 3, 4 and 5** are relatively small. This might have impinged on the results, as we were not able to stratify the samples by age, type of device or site. As the clinical and psychological care of LVAD patients might slightly differ between the sites this could have lead to an unknown bias in the prevalence of psychological distress.

The limitations in **Chapters 8, 9 and 10** included the relatively young age of the patients and the fact that most patients were NYHA class I-II, thereby possibly affecting the association with inflammatory markers. Overall, there was a low prevalence of female participants in the heart failure samples included in this dissertation, therefore caution has to be taken in generalizing these results to female patients. Furthermore, patients and partners who refused to participate in the study might have suffered from more psychological distress, with the possibility that the prevalence of psychological distress in this dissertation could be an underestimation of the actual situation.

Measurements and statistical analyses

Throughout this dissertation multiple constructs were used to measure psychological distress. Except for **Chapter 6**, which used a clinical diagnosis of depression, all other studies used self-report questionnaires. Although even minimal symptoms of distress have been related to prognosis in cardiac populations[4] and the instruments we used have been validated in cardiac samples, their sensitivity and specificity are still lower compared to a clinical diagnosis of psychological disorders.[5, 6] Also, the items in these instruments do not tap into the subtypes of psychological disorders and do not inquire about the duration of symptoms. In addition, the different instruments used for measuring depression and positive affect assess slightly different aspects of the same constructs **(Chapter 8 and 10).**

The clinical data gathered for all studies were not self-reported but extracted from the patients' medical records. Although medical records a more reliable than self-reported clinical data, researchers are still dependent on the quality of the diagnostics and registration inherent to the systems used in the hospitals. Using the medical records, extensive information could be gathered on the anamneses and etiology of the patients' heart failure, echocardiography, electrocardiogram, blood tests, complications, hospitalizations and medication. The cytokine measurements, which were used for the studies in **Chapters 8-11** were performed by a specialized lab, with highly experienced staff

an high quality assays. However, due to missing blood samples or detection limits, missing a small percentage of cytokine data was inevitable. The missing cytokine data were imputed, thereby taking into account the detection range of the assays **(Chapters 9, 10 and 11)**.

In the present dissertation, a variety of statistical analyses was used, including survival analysis, logistic and linear regression, mixed linear modeling, multilevel analysis and univariate and multivariate analysis of covariance, to examine predictors of binary and continuous outcomes or time-to-event data. Based on current theoretical evidence, we adjusted the analyses for potential clinical, psycho-social and socio-demographic confounders. However, there is always residual confounding caused by the fact that information on potential confounders were lacking or poorly assessed. Furthermore, except for **Chapter 6**, the sample size in some of the studies did not allow for the addition of many predictors in order to prevent overfitting of the models, which may yield overly optimistic results.[7] To avoid or minimize overfitting the optimal statistical strategy for each study was carefully considered. By using mixed linear modeling and multilevel analyses all available time points were used for each patient thereby limiting bias and preserving statistical power **(Chapters 3, 4, 10, 11)**. Furthermore, if possible the number of predictor variables in the models was reduced by combining predictors (i.e. Charlson Comorbidity Index) into a single composite measure **(Chapters 3, 4 and 5)**. While this approach preserves degrees of freedom in the model, this comes at a trade-off, as specific information about the individual components of the composite measure is lost.[7] Hence, while it appears our studies did not violate any guidelines regarding overfitting, caution was maintained in formulating any strong conclusions where appropriate.[8]

PRACTICAL AND CLINICAL IMPLICATIONS

Use of patient-reported outcomes to improve patient care

During the last few years, there has been growing interest in the patient perspective by policy makers, physicians and other health care professionals. The *American Institute of Medicine, American College of Cardiology* and the *European Society of Cardiology* have stipulated that future medical treatment should fulfill the key aspects of being safe, effective, timely, equitable, efficient and *patient-centered*.[9] The patient perspective should guide clinical trials and patient care in order to provide the most optimal health care system of the 21st century. In patient-centered care, assessment of the patient perspective, by means of

asking patients to rate their own health, can aid with the identification of high risk patients and clinical decision making, but also in optimizing clinician-patient communication and removing barriers to patient self-management. Information on the patient perspective provides the opportunity to take into account patients' needs, preferences and psychological make-up in addition to their clinical profile and may provide evidence-based information for patients who want to make informed treatment options.[10]

In this dissertation, we evaluated the patient perspective by means of standardized and validated questionnaires that tap into psychological distress and health status. Findings from the current dissertation **(Chapter 3, 4)** and previous research **(Chapter 2)** indicate that the prevalence of anxiety, depression and PTSD in LVAD patients and their partners shortly after LVAD implantation is between 23-48%.[11, 12] A small number of LVAD patients seem to suffer from chronic levels of distress, and these patients seem to have more difficulty adjusting to life post LVAD implantation and are at high risk of poor self-care behavior. Patients implanted with a LVAD experience an increase in health status scores post implantation, which is consistent with those found in other large scale trials,[13-17] indicating that the consequences of LVAD therapy are similar across sites and countries. However, our findings also showed that LVAD patients still have decreased health status compared to the Dutch normative population and patients who have undergone heart transplantation.[18-20] Hence, although LVADs may solve the problem of donor scarcity, it is important not to lose sight of the impact of treatment on patients and thus continue to seek ways that may help improve their well-being and quality of life.

Although **Chapters 2-5** do not examine the relation between psychological distress and cardiovascular outcomes, **Chapters 6 and 7** and previous literature show that poor health status and psychological distress are independent risk factors for mortality and hospital readmissions in various cardiac populations.[21] This relation can partially be explained by behavioral factors such as lack of adoption of secondary prevention behaviors (i.e. smoking cessation, physical activity) and an increase in inflammation. As shown in **Chapters 10 and 11**, this effect on inflammation can be counteracted by an increase in health status and positive affect.

Overall, the high prevalence of psychological distress in heart failure patients should gain more awareness in order to prevent adverse outcomes. As psychological guidance or interventions are often not available for patients with heart failure, many patients are given

anti-depressants when presenting with psychological distress.[22] However, **Chapter 7** shows that caution should be used when prescribing anti-depressants, as they do not guarantee a reduction in cardiovascular events and might even increase the risk for heart failure mortality through unknown pharmacological, physiological or behavioral mechanisms,[23, 24] depending on the type of anti-depressant and duration of use.

Challenges of using patient-reported outcomes in clinical practice

Despite their clear benefits, the use of patient-reported outcomes is also associated with considerable challenges.[25] Hence, when choosing a measure to assess patient-reported outcomes, it is important to make a well informed decision. With respect to health status, generic measures, such as the Short-Form Health Survey (SF-12 or SF-36), are suitable for all populations and can therefore be used to compare heart failure patients with a normative population or patients with other conditions.[26] However, as these measures may not be sufficiently sensitive to tap into treatment-related changes the use of disease-specific measures is often preferred.[27] The Minnesota Living with Heart Failure Questionnaire (MLHFQ)[28, 29] and the Kansas City Cardiomyopathy Questionnaire (KCCQ)[30] **(Chapters 2, 4, 11)** have been developed for use in heart failure patients and include questions on functional limitations and symptoms specific to heart failure. Both measures are subject to copyright but are easy to administer and have proven to be psychometrically sound and predict heart failure prognosis.[31,32] It is important to consider that for LVAD patients the MLHFQ and KCCQ may still be too time-, or energy-consuming just before or after LVAD implantation. Furthermore, a recent study found that baseline KCCQ levels were not predictive of survival after LVAD implantation.[33] It is possible that change in health status over time rather than pre-implantation health status is a more valuable predictor of clinical outcome, as we examined in **Chapter 4**.

With respect to the assessment of psychological distress, such as anxiety and depression, a large number of scales are available, but they cannot necessarily be used interchangeably due to differences in prevalence rates.[6,34] Besides the Hospital Anxiety and Depression Scale, Beck Depression Inventory and the Center for Epidemiological Studies Depression Scale, the more recent Patient Health Questionnaire (PHQ-9) and Generalized Anxiety Disorder (GAD-7) **(Chapter 5)** are considered reliable measures that are free of charge and easy to administer.[35-37] In addition to the assessment of negative emotions, there

has been an increased interest in the assessment of positive emotions, such as positive affect, optimism, and self-esteem **(Chapter 10)**. Given that positive and negative affect are not merely the opposite of a continuum,[38, 39] and that both types of affect can be present simultaneously, their assessment might contribute to a fuller understanding of the contribution of psychological factors in heart failure patients.

In addition to the choice of measure used, there are important challenges associated with the analysis and interpretation of scores. First, in order to evaluate the efficacy of a treatment, as in **Chapters 4 and 11,** it is important to know which change in scores represents a clinically significant change (e.g. 5 points on the KCCQ).[31] Second, for most measures of psychological distress a continuous and dichotomous score can be calculated, the latter being based on a cut-off score with the highest sensitivity and specificity for detecting the psychological disorder. Using a dichotomous score may enhance the clinical interpretability while creating a potential loss of important information. Third, instead of analyzing only between-person differences in scores over time there should be an increased focus on within-person differences in scores over time and the predictors of these changes. Such information may help to identify patients at high-risk for a difficult post-treatment course and adverse health outcomes **(Chapter 4).**

In addition to the choice of measure and the analytical strategies used, there are important practical, methodological and attitudinal barriers for implementing measures on health status and psychological distress in clinical practice. Lack of financial and human resources and especially the perceived relevance by health care providers are preventing the large scale use of these measures in heart failure care.[40,41] Future studies in heart failure patients are therefore warranted to make the measures more actionable, efficient and user-friendly, but also more easy to interpret.[25]

Patient-reported outcomes, heart failure and health outcomes: How are they tied together?

Several mechanisms have been proposed that may explain the association between psychological distress and adverse health outcomes, such as hypothalamic-pituitary-adrenal (HPA) axis dysfunction, autonomic nervous system imbalance, platelet activation, adverse health behaviors and inflammation.[42-45] **Chapters 9-11** of this dissertation focused on the association between patient well-being and inflammation in different samples of heart failure patients, while also taking into account lifestyle behaviors. The relation between

psychological distress and inflammation is considered to be bidirectional,[46] with inflammation preceding distress while distress may also precede inflammation. Various hypotheses have been formulated which suggest that pro-inflammatory cytokines are able to induce depression through HPA-axis hyperactivity and serotonin shortage.[47-51] However, studies examining these hypotheses found mixed results.[52-58] **Chapter 9** of this dissertation adds to this body of evidence, as we found no association between inflammation and depressive symptoms in patients with heart failure.

Alternatively, evidence suggests that the immune system can respond to psychological distress in an immunopathological manner which results in chronic inflammation. The results presented in **Chapters 10 and 11** showed that this effect on inflammation may be reversed by the presence or increase in patient well-being, suggesting that positive emotions may represent unique components of psychobiological resilience.[59] Interestingly, while there is strong evidence for a link between patient well-being and inflammation, **Chapters 8 and 11** found no association between psychological distress, health status and BNP or NT-proBNP, indicating that these cardiac markers may be more closely related to disease severity than to psychological distress.

The association between psychological distress and inflammation seem to be strongly dependent on the sample composition, sampling method (i.e. clinical vs. community) and methodology. For example, a clinical diagnosis of depression seems to be more strongly related to inflammation than depressive symptoms, as measured by self-reported questionnaires.[46] Furthermore, evidence on depression and anxiety suggest that the type of symptoms, clinical subtype of the disorder, and onset of the disorder may influence the relation with inflammation.[60,61] The association between psychological distress and inflammation may mainly be driven by somatic symptoms of depression and anxiety rather than by cognitive symptoms.[53] For depression, three clinical subtypes have been identified (i.e. catatonic, melancholic and atypical). The atypical depression subtype, which is marked by hypersomnia, fatigue and weight gain, seems to induce metabolic syndrome (i.e. elevated blood pressure, abdominal obesity) and higher levels of inflammation.[62-64] Melancholic depression, which is marked by psychomotor disturbance, insomnia and weight loss, induces hypercortisolemia.[65] The association between major depressive disorder, dysthymia and inflammation (i.e. IL-1β, IL-6, TNFα) show inconclusive results.[66] These subtypes of depression are likely to contribute to the variability in associations with biological measures

and suggest that there may be a dose-response relationship between psychological distress and inflammation. In relation to the onset of depression, current evidence indicates that the association between depression and inflammation is more apparent in those who suffer from recurrent depression than in patients with a single episode of depression.[67, 68] Contrary to acute stress, cortisol released through the HPA-axis response in chronic stress induces an upregulation of inflammation and the sympathetic nervous system.[69]

To gain more insight into the psycho-neuro-immunological mechanisms linking psychological distress and health outcomes in patients with heart failure, more large-scale studies should address the heterogeneity of psychological distress. Furthermore, studies should examine the relation between different types of psychiatric disorders (generalized anxiety disorder, major depressive disorder, dysthymia, atypical depression, new-onset vs. recurrent depression) and their relation with inflammatory markers, behavioral factors and disease progression, thereby taking into account socio-demographic, socio-economic and personality factors. This will give us insight into the physiological distinction between heart failure patients suffering from psychological distress, resulting in the ability to better predict heart failure disease trajectories and to provide more effective psychological treatment options resulting in better treatment outcomes.

Management and treatment of distressed heart failure patients

Based on the current literature, monitoring psychological distress might not be beneficial due to a trade-off between the sensitivity and specificity of the screening instruments.[6] Furthermore, only a paucity of studies has evaluated psychological and pharmacological interventions in heart failure patients. The efficacy of interventions using education, telemonitoring and telephone support to improve patient-well being are mixed,[70-73] as are interventions using cognitive behavioral therapy (i.e. identifying and challenging negative automatic cognitions and behaviors) as mainstay.[74] By contrast in studies on ICD patients - that also include heart failure patients - cognitive behavioral therapy has shown to be effective in reducing psychological distress and improving health status.[75-77] Interventions using exercise training showed a positive effect on quality of life in heart failure patients but not on anxiety or depression,[78-80] while relaxation and mindfulness showed only short-term improvements in anxiety and depression.[81, 82] Combining different types of interventions did

not alter these findings.[83, 84] A recent multi-model intervention in LVAD patients, consisting of nutrition management, exercise training and psychosocial support, also found no impact on health status, anxiety and depression compared to a control group.[85] Overall, various factors may be responsible for the small effect sizes of intervention studies such as competing priorities of the patients, the stigma of psychological distress, the financial and resource-intensive design of the interventions and by incorrectly addressing psychological distress (e.g. depression) as a homogeneous disorder.

Also pharmacological studies have found only small positive effects on depression in patients post myocardial infarction or with stable coronary heart disease.[86-90] However, two seminal studies on patients with heart failure did not find an effect of citalopram or sertraline on depression nor any effects on cardiovascular outcomes.[91, 92] Hence, based on this evidence and the results from **Chapter 6**, the value of psychopharmacological therapy in patients with heart failure remains uncertain, and psychotropic medication should only be administered after careful evaluation by a heart failure specialist. One has to keep in mind that different antidepressants can have a differential impact on inflammation and metabolic dysregulation,[93] while inflammation and metabolic dysregulation may also impact on the efficacy of antidepressant use.[60] Furthermore, it is important to discuss patients' preferences for psychological versus pharmacological treatment when offering a treatment in order to enhance patient compliance.

In order to provide effective treatment for heart failure patients suffering from psychological distress in the future, it is important to address the heterogeneity of psychological distress, to integrate needs and preferences of the individual patient and use a collaborative care approach in which primary care providers, cardiologists, heart failure nurses, and mental health professionals work together to provide optimal care and monitor patients' progress. As addressed in **Chapter 3** of this dissertation it is also very important to involve the partner in these interventions, as they may also suffer from severe distress which can have adverse effects on the health of the patient. Furthermore, getting patients involved regarding their own treatment by means of shared decision making is essential, as the efficacy of an intervention is greatly dependent on the motivation of the patient. A stepped care approach, in which patients can receive different types and intensities of services, might also help in providing the patient different alternatives depending on their own preferences and needs. This will eventually lead to the tailoring of interventions.

Future perspective

This dissertation extends previous research on health status and psychological distress in patients with an ICD, CRT-D or LVAD. Including measures on the patient perspective is paramount in order to optimize patient-centered care and to bridge the gap between research and clinical practice. However, there is still much ground to be gained, with recommendations for future research and clinical practice outlined in **Table 1.**

First, future research should enhance the knowledge on the well-being of LVAD patients using large scale prospective observational studies. LVAD therapy provides patients with end-stage heart failure a chance of survival and a better quality of life while waiting for a donor heart. However, dealing with device-, driveline- and medication related aspects of a LVAD remains challenging. The impact of LVAD therapy on patients' lives is reflected in the citations below.

Man (59 years) "Slowly I start to feel myself again and once in a while I even forget I have a LVAD. However, I do realize my life hangs by a thread (literally and figurative)".

Man (41 years) "My LVAD was implanted in an emergency care setting, I was therefore not able to choose whether I would want a LVAD. However, if they would have asked me again today I would have said YES".

Female (53 years) "Since I got the LVAD I can lead a normal life again. I am happy with my LVAD, it has become a part of me. However, I do look forward to having a heart transplant so that I no longer have any restrictions with playing sports, showering and swimming".

The success of LVAD therapy has generated debate about the severity of heart failure that should prompt implantation of the device, thereby increasing the group of patients who may benefit from this treatment.[94] To deal with this growing group of patients it is crucial to gain insight into the complex nature of psychological distress associated with having an LVAD, including information on illness perceptions, personality, coping and social support but also on factors that may enhance adjustment such as optimism. Furthermore, research should shift its focus from presenting mean group changes of patient well-being scores to examining individual score trajectories. This dissertation showed large differences in

individual health status score trajectories which are only partially explained by measures of disease severity pre-LVAD, comorbidity and psychological distress. Identifying the predictors of these trajectories is crucial in order to better predict the post-implantation course, enhance the quality of care and improve the outcomes after LVAD therapy. Furthermore, LVAD patients and their partners who show chronic levels of anxiety and depression should be closely monitored and offered additional care.

Second, in order to develop more efficient psychological interventions for heart failure patients it is important to enhance our understanding of the behavioral and biological pathways underlying the relationship between patient well-being and health outcomes. Research should focus on whether heart failure patients with different profiles of psychological distress show different pathophysiological characteristics, disease trajectories and outcomes (i.e., mortality, hospitalization) and arguably need different treatment options. This will provide the opportunity to tailor interventions to patients' needs and increase the quality of care.

Third, to increase the feasibility of measuring patient well-being and providing additional psychological care to heart failure patients, several issues have to be tackled. To save time and human resources it is important to examine rapid and efficient ways to administer, score and interpret scores on patient-well being. This can be done using new technologies (i.e. computerized assessment and scoring, mobile phone applications) that enables patients to complete measures at home or while they are waiting at the outpatient clinic. Although the current generation of heart failure patients might not yet be sufficiently acquainted with this technology, this will be an option in the near future. For the small group of heart failure patients who show signs of chronic distress, additional care or interventions should be in place to prevent adverse health outcomes. It is important to discuss with the patient the options for psychological treatment within or outside the hospital and start by providing additional care using a stepped-care approach (i.e. (web-based) educational session or relaxation therapy). The challenge will be to keep such patient care feasible in terms of human and financial resources in order to enhance the possibility that such interventions will become an integrative part of the clinical care of heart failure patients.

Hopefully, the new insights from this dissertation and the recommendations for future research and clinical practice will help shed light on the pathophysiological processes involved in heart failure, improve risk stratification of distressed patients and lead to the

development of effective multi-disciplinary interventions that will enhance survival and improve patient well-being.

Table 1: Recommendations for future research and clinical practice

Future research	Clinical practice
• Examine rapid and efficient ways to administer, score and interpret outcomes on patient well-being in clinical practice	• Use disease-specific health status and distress questionnaires to measure patient well-being in heart failure samples.
• Use (computerized) serial assessments • Use outcomes on patient well-being as primary outcomes in large-scale, well-designed clinical trials	• Create awareness of the importance of patient-wellbeing in relation to clinical outcomes, treatment expectations, self-management and patient-physician communication
• Examine behavioral and biological mechanisms underlying the relationship between psychological distress and adverse clinical outcomes	• Provide additional (psychological) care to patients whose health status and psychological distress do not improve after treatment
• Address the heterogeneity of psychological distress in heart failure patients	• Provide patient-centered care as much as possible

• Examine the most appropriate timing of psychological interventions and relative efficacy of different interventions which focus on:
  • including exercise training and mindfulness components
  • patient tailored interventions using a stepped-care approach
  • including the patient's family (partner, children)
  • web-based interventions
	• Include a mental health professional in the multi-disciplinary heart failure team who has sufficient knowledge of heart disease and device therapy; if this is not possible refer to a mental health professional in the patients' local environment

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CHAPTER 13

Nederlandse samenvatting, dankwoord en curriculum vitae

NEDERLANDSE SAMENVATTING

Hartfalen is een chronische aandoening waarbij het hart niet meer in staat is om voldoende bloed rond te pompen om aan de behoefte van de weefsels te voldoen, en wordt gekenmerkt door vermoeidheid en kortademigheid bij geringe inspanning. Oorzaken van hartfalen zijn een hartinfarct, hoge bloeddruk, een defect aan de hartkleppen, een hartritmestoornis of cardiomyopathie ('hartspierziekte'). Cardiomyopathie kan verworven zijn (bijv. door alcoholgebruik of een infectie) of genetisch van aard zijn. Hartfalen is een veelvoorkomende aandoening met een hoge mortaliteit.

Er bestaan verschillende behandelopties voor hartfalen afhankelijk van de ernst van de aandoening, zoals medicatie, een implanteerbare cardioverter defibrillator (ICD), eventueel met resynchronisatie therapie (CRT-D), of een linker ventrikel assist device (LVAD). Een ICD registreert continue informatie over het hartritme en beëindigt eventuele hartritmestoornissen met snelle elektrische pulsen of een krachtige elektrische schok. Een CRT-D kan naast het beëindigen van hartritmestoornissen ook de pompfunctie van het hart verbeteren door met elektrische impulsen de linker- en rechterventrikel weer synchroon te laten samentrekken. Een LVAD zorgt voor een mechanische ondersteuning bij eindstadium hartfalen en dient als (tijdelijke) vervanging van harttransplantatie.

Hartfalen kan een enorme invloed hebben op het fysieke, sociale en psychologische welbevinden van patiënten. Hierdoor hebben patiënten met hartfalen vaak een lagere kwaliteit van leven en lijden ze vaker aan psychische klachten zoals angst en depressie. Eerder onderzoek heeft aangetoond dat het ervaren van psychische klachten kan leiden tot een hogere mortaliteit, meer ziekenhuisopnames en een lagere therapietrouw. De link tussen psychische klachten en slechtere gezondheidsuitkomsten kan gezocht worden in gedragsmatige en fysiologische factoren zoals het niet naleven van medicatie en levensstijl voorschriften (bijv. minder alcoholgebruik en meer lichaamsbeweging) en een verhoogde inflammatie. Inflammatie is een biologische reactie van het lichaam op stress, waarbij moleculen (cytokines) vrijkomen die het hartfalen kunnen verergeren.

Als gevolg van deze bevindingen zijn naast klinische factoren ook patiëntgerapporteerde uitkomsten (bijv. kwaliteit van leven) van steeds groter belang. Patiëntgerapporteerde uitkomsten zijn uitkomsten van vragenlijsten die door patiënten zelf worden ingevuld. Deze lijsten gaan bijvoorbeeld over de symptomen die patiënten ervaren, hun lichamelijk en mentaal functioneren en hun kwaliteit van leven. Het gaat dus om de

beleving van de patiënt ten opzichte van hun ziekte en/ of behandeling. Deze uitkomsten kunnen leiden tot een hogere kwaliteit van zorg doordat hiermee patiënten beter geïnformeerd kunnen worden over de gevolgen van een behandeling, en patiënten met langdurige of ernstige psychische klachten op tijd geïdentificeerd en geholpen kunnen worden. Bovendien kunnen de uitkomsten gebruikt worden om de effectiviteit van behandelingen te vergeleken en biedt het de mogelijkheid tot een meer individuele patiëntenbenadering.

DOEL VAN DIT PROEFSCHRIFT

In dit proefschrift is onderzoek gedaan naar de psychosociale aspecten van het leven met hartfalen (na een implantatie van een CRT-D of LVAD), de relatie tussen psychische klachten, inflammatie en mortaliteit en de determinanten van psychische klachten bij hartfalen patiënten. Om een beter beeld te krijgen van de psychosociale aspecten ligt de focus van dit proefschrift op patiëntgerapporteerde uitkomsten.

In **deel 1 (Hoofdstuk 2-5)** van dit proefschrift wordt een literatuuroverzicht gegeven van de gezondheidstoestand en psychische klachten van patiënten met een LVAD. Ook worden hierin de resultaten beschreven van een prospectief onderzoek onder LVAD patiënten en hun partners waarbij naar het verloop van gezondheidsstatus en psychische klachten wordt gekeken over de tijd, en de determinanten hiervan. Daarnaast wordt en in dit deel gekeken naar het aandeel van symptomen versus genetische belasting op gezondheidsstatus en psychische klachten bij patiënten met genetisch hartfalen (non-compaction cardiomyopathie).

In **deel 2 (Hoofdstuk 6 en 7)** wordt met een literatuurstudie en een grote Deense patiënten dataset gekeken naar het verband tussen psychische klachten, het gebruik van antidepressiva en morbiditeit en mortaliteit.

In **deel 3 (Hoofdstuk 8-11)** wordt gekeken naar de relatie tussen gezondheidsstatus, psychische klachten en inflammatie bij verschillende groepen hartfalen patiënten. Hierbij wordt onderzocht in welke mate psychische klachten onafhankelijk zijn van de mate van ziekte ernst, of inflammatie een etiologische factor is in het ontstaan van depressie bij hartfalen patiënten, en of een verbetering in gezondheidsstatus en psychische klachten ook inflammatie kan verlagen.

VOORNAAMSTE BEVINDINGEN VAN DIT PROEFSCHRIFT

LVAD therapie wordt pas sinds enkele jaren op grote schaal toegepast als vervanging van harttransplantatie of brug-naar-transplantatie bij hartfalen patiënten. Hierdoor is er nog relatief weinig bekend over de psychosociale gevolgen van deze behandeling. Uit de bestaande literatuur **(Hoofdstuk 2)** en de ervaringen uit de dagelijkse praktijk **(Hoofdstuk 3 en 4)** blijkt dat LVAD patiënten een sterke verbetering laten zien in gezondheidsstatus na de implantatie, onafhankelijk van het type LVAD en de implantatie strategie (urgent of semi-selectief). Echter lijkt de gezondheidsstatus van de patiënten wel te stabiliseren na 3 tot 6 maanden, en is er een grote mate van verschil tussen patiënten in het beloop van de scores welke maar deels werd verklaard door de ernst van de ziekte, co-morbiditeit en psychische klachten. Bovendien lijkt een deel van de LVAD patiënten psychische klachten zoals angst, depressie en post-traumatische stress (PTSD) te hebben, vooral kort na implantatie. Deze klachten lijken vaak het gevolg te zijn van complicaties, langdurige ziekenhuisopnames en vereiste LVAD trainingen. Ook de partners van de LVAD patiënten blijken een hoge mate van psychische klachten te ervaren, welke soms zelfs hoger zijn dan bij de LVAD patiënten zelf.

Het welzijn van patiënten met non-compaction cardiomyopathie, welke in **Hoofdstuk 5** in beeld wordt gebracht, is tevens nauwelijks eerder onderzocht. Uit **Hoofdstuk 5** blijkt dat de score op gezondheidsstatus en mate van psychische klachten bij non-compaction cardiomyopathie patiënten (NCCM) voornamelijk afhankelijk zijn van de symptomen van hartfalen en de daaruit voortvloeiende beperkingen en behandelingen (bijwerkingen van medicatie) en niet gerelateerd zijn aan de genetische belasting van de aandoening. Deze resultaten lijken aan te geven dat genetische screening voor hartfalen een geringe negatieve invloed heeft op het leven van patiënten, maar dat het wel van belang is nog meer onderzoek te doen naar de eventuele effecten van psychische klachten op het beloop van NCCM en andere erfelijke hartaandoeningen.

Het belang van het identificeren van een slechte gezondheidsstatus en psychische klachten blijkt uit de resultaten van **Hoofdstuk 6 en 7** waarin een relatie wordt gevonden tussen psychische klachten, het gebruik van antidepressiva en een slechtere prognose en overleving. Hieruit blijkt verder dat men voorzichtig moet zijn met het voorschrijven van antidepressiva, vooral bij subklinische depressie, totdat er meer bekend is over de farmacologische, fysiologische en gedragsmatige mechanismen die verantwoordelijk zijn voor de relatie tussen psychische klachten en een slechtere overleving.

Een van de mechanismen die in **Hoofdstuk 9-11** verder is onderzocht is inflammatie. In de literatuur wordt vaak gesproken over een bi-directionele relatie tussen inflammatie en depressie, waarbij inflammatie depressie veroorzaakt en depressie leidt tot een hogere inflammatie. In **Hoofdstuk 9** is onderzocht in welke mate depressie bij hartfalen patiënten geassocieerd is met inflammatie, ziekte ernst en persoonlijkheidsfactoren (Type D persoonlijkheid). Hieruit blijkt dat Type D persoonlijkheid een sterkere voorspeller was van depressie dan inflammatie en ziekte ernst. Het kan dus zo zijn dat slechts in een deel van de hartfalen patiënten inflammatie leidt tot depressie, of dat depressie eerder inflammatie voorspelt dan andersom. Verder is het van belang het onderzoek te herhalen met een uitgebreider scala aan psychosociale en gedragsmatige factoren.

Uit de assumptie dat depressie een negatieve invloed heeft op inflammatie vloeit voort dat wellicht positieve emoties, zoals optimisme en een betere gezondheidsstatus ook inflammatie zouden kunnen verlagen. In **Hoofdstuk 10** blijkt inderdaad dat het ervaren van meer positieve emoties significant geassocieerd is met een lagere inflammatie (sTNFr2, TNFα, IL-6). Wel was de relatie tussen positieve emoties en inflammatie afhankelijk van het type instrument dat werd gebruikt om positieve emoties te meten. Dit geeft aan dat de positieve emoties die deze instrumenten meten niet identiek zijn.

Hoofdstuk 11 laat zien dat patiënten die na een CRT-D implantatie verbetering ervaren in gezondheidsstatus ook een daling laat zien in de inflammatoire marker TNFα maar niet bij de andere markers. Verder bleek gezondheidsstatus niet geassocieerd te zijn met het cardiale hormoon brain natriuretic peptide (BNP). Het ontbreken van een relatie tussen objectieve parameters voor de ernst van hartfalen en patiënt-gerapporteerde uitkomsten werd al eerder gevonden in **Hoofdstuk 8.** Patiëntgerapporteerde uitkomsten lijken dus onafhankelijk te zijn van de ziekte ernst en moeten daardoor beschouwd worden als belangrijke risicofactoren voor de prognose van hartfalen. Uit **Hoofdstuk 11** blijkt bovendien dat er een grote discrepantie zit tussen de verbetering van patiënten op gezondheidsstatus en de verbetering op de echocardiografie. Zo zijn er patiënten bij wie het hartfalen volgens de resultaten van de echo is verbeterd, maar die zelf geen verbetering ervaren, en andersom. Een verbetering op de echocardiografie was niet geassocieerd met inflammatie maar wel met het cardiale hormoon brain natriuretic peptide (BNP), waarvan de waarde stijgt bij overbelasting van het hart.

CONCLUSIES EN AANBEVELINGEN

De bevindingen in dit proefschrift bevestigen het belang van patiëntgerapporteerde uitkomsten in hartfalen. De vooruitstrevende behandelmethoden van deze tijd maken het mogelijk een stijgend aantal patiënten met hartfalen in leven te houden en hun kwaliteit van leven te verbeteren. Hoewel het merendeel van de patiënten goed omgaat met een ICD, CRT-D of LVAD rapporteert een subgroep (≈25%) van deze patiënten psychische klachten (angst, depressie) welke kunnen leiden tot een slechtere prognose en vroegtijdig overlijden. Om dit te voorkomen is het van belang om patiëntgerapporteerde uitkomsten mee te nemen in de dagelijkse zorg van hartfalen patiënten om zo alert te zijn op eventuele psychische problemen en deze op tijd te behandelen. Verder is het meten van patiëntgerapporteerde uitkomsten ook een meerwaarde voor de kwaliteit van de zorg omdat het patiënten perspectief niet is af te leiden uit het medische dossier maar wel van groot belang kan zijn voor de arts-patiënt communicatie en het voorspellen van behandeluitkomsten. Verder biedt het meten van deze uitkomsten de mogelijkheid tot een patiënten benadering waarbij een arts het patiënt perspectief en de wensen en voorkeuren van een patiënt kan afwegen tegen de risico's van verschillende behandelopties.

Het implementeren van patiëntgerapporteerde uitkomsten in de dagelijkse zorg van hartfalen patiënten is echter niet eenvoudig, vooral vanwege praktische aspecten zoals financiële middelen, de tijd en arbeidskracht die nodig is om de gegevens te verzamelen en te analyseren. Het is dus van belang dat toekomstig onderzoek zich richt op hoe patiënt gerapporteerde uitkomsten zo eenvoudig en efficiënt mogelijk kunnen worden toegepast (web-interventies, digitale testafnames). Ook moeten er meer onderzoek gedaan worden naar interventies voor hartfalen patiënten met psychische klachten waarbij rekening gehouden wordt met de heterogeniteit van de psychische klachten en de wensen van de patiënt. De heterogeniteit van psychische klachten kan namelijk samenhangen met specifieke biologische (inflammatie) en gedragsmatige mechanismen en ziekte beloop, waarvoor verschillende behandelopties nodig kunnen zijn. Verder is het van belang om te streven naar een multidisciplinair behandelteam waarbij patiënten met psychische klachten hulp kunnen krijgen van een maatschappelijk werkster of een psycholoog die voldoende kennis heeft van de specifieke problemen geassocieerd met het hebben van een ICD, CRT-D of LVAD. Hierbij is het aan te bevelen om ook de partners en andere familieleden van de patiënten te betrekken omdat ook zij vaak kampen met psychische klachten die een

negatieve invloed zouden kunnen hebben op de gezondheid van de patiënt.

Bij het gebruik van patiëntgerapporteerde uitkomsten dient een breed scala aan constructen meegenomen te worden om zo de complexiteit van psychische klachten in hartfalen patiënten te kunnen doorgronden. De keuze voor een bepaalde vragenlijst moet hierbij zorgvuldig worden afgewogen, afhankelijk van het doel (screening, kost-effectiviteit of behandeluitkomsten meten) en het gebruiksgemak (aantal subschalen, interpretatie scores). Vooral persoonlijkheid, coping, sociale steun, optimisme en levensstijl factoren (bewegen, roken, drinken) zijn hierbij van belang. In plaats van het bekijken van groepsgemiddelden op patiëntgerapporteerde uitkomsten is het van belang individuele score verloop te bekijken, en te zien hoe deze worden beïnvloedt.

Hopelijk zullen de inzichten van dit proefschrift en de aanbevelingen voor toekomstig onderzoek en praktijk helpen om de mechanismen tussen psychische klachten, biologische en gedragsmatige factoren en overleving te ontrafelen, patiënten met een hoog risico op psychische klachten op tijd te identificeren en succesvolle interventies te ontwikkelen die de zorg en overleving van patiënten met hartfalen kunnen verbeteren.

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